ACTA RADIOLOGICA
EDITA IUSSU SOCIETATUM RADIOLOGICARUM
DANIAE, FENNIAE, NORVEGIAE ET SUECIAE

VOL. 47 FEBRUARY 1957 FASC. 2

INTRACARDIAC PRESSURE CHANGES WITH RAPID FLUID INJECTION INTO THE RIGHT HEART

by

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The purpose of this study was to collect data on the changes in pressure within the right heart, produced during a procedure comparable to selective angiocardiography.

A similar study of the intracardiac pressure changes in intravenous angiocardiography has been carried out previously (1). In these experiments physiologic saline solution and contrast material were injected into a brachial vein in dogs during 0.5 to 1 second. No pressure changes were found in the superior vena cava or in the right heart when 50 ml Ioduron 70 %, or the same amount of physiologic saline solution, was injected.

The present study has been made in ten dogs under intraperitoneal sodium pentobarbital anesthesia.

Equipment and experimental procedure. A No. 8 cardiac catheter was introduced in a jugular vein and advanced to the right ventricle or right atrium for pressure measurements. It was connected to a strain gauge pressure recording instrument. Simultaneous recording of the respiration was performed by electrokymographically recording the variations of roentgen ray transmission through the lung. An electrocardiogram (lead II) was also recorded.

For the injection of physiologic saline and contrast material a recoil-free No. 10 catheter was introduced through the same vein as the catheter for pressure recording. For rapid injections a pneumatic pressure syringe was used. The injection was completed between 0.3 and 0.5 seconds, and the duration of the injection was recorded by a previously described

Submitted for publication 11 June 1956.

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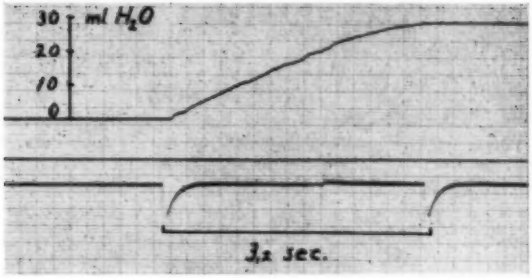

Fig. 1. Time-volume curve for injection of water by pressure syringe through heart catheter recorded by means of an electrokymograph. Decrease in injected volume of fluid per time unit seen during last part of injection stroke.

electric indicator (3). In this device the plunger of the syringe activates a microswitch at the beginning of the injection, and a second similar switch at its termination, a brief pulse-like signal being recorded on the electrocardiographic tracing.

Pressure, respiration, and electrocardiographic recordings have been made by means of an Elema direct-writing jet recorder (Mingograph 24).

For each experiment one ml of physiologic saline solution per kg body weight was injected on 4 separate occasions with approximately 15 to 20 minutes between the injections. Two injections of the same volume of Urokon 70 % were then made.

Preliminary calibrations of equipment. The pressure syringe was studied with respect to the volume of fluid injected per unit of time. A 50 ml glass syringe with eccentric outlet was placed vertically in a stand. The pressure syringe and the glass syringe were connected through a No. 10 cardiac catheter 100 cm in length, which for this purpose was provided with Luer-Lok connections at both ends. A narrow central roentgen ray beam was directed along the central axis of the glass syringe. The decrease in roentgen ray transmission by the glass syringe and its contents when water was injected from the pressure syringe into the glass syringe was then recorded by the photocell of the electrokymograph. Fig. 1 shows the recording obtained by the injection of 30 ml of water during 3.7 seconds. The shape of the curve was essentially the same, that is to say almost a straight line, with other injections of varying pressure and volume. In any case, the volume of fluid injected per second was considered to be satisfactorily distributed throughout the whole injection.

The time of the duration of the injection as recorded over the ECG circuit was controlled as follows. A cardiac catheter, 100 cm in length,

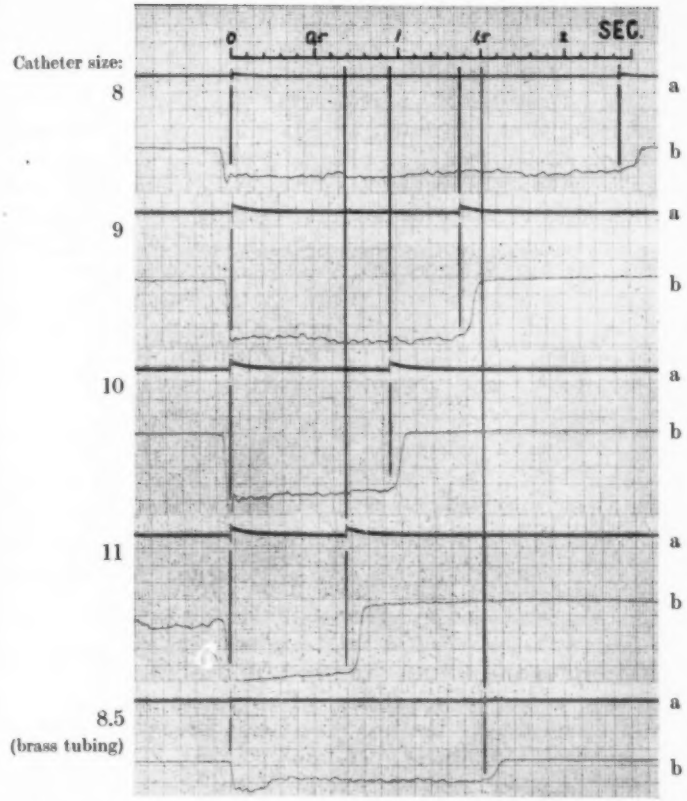

Fig. 2. Comparison between electric indication (a) obtained by activation of microswitches by plunger of syringe and densometric recording (b) of appearance and disappearance of contrast material at tip of catheter. Four heart catheters and one piece of brass tubing are tested at same injection pressure and contrast volume. Indications of beginning and end of injection for each catheter do not fully coincide. Type of deflection in densogram principally the same on injection through heart catheters and brass tubing.

was connected to the pressure syringe. The distal part of the catheter was firmly held in the horizontal position in a stand and the central beam of the roentgen ray directed perpendicularly to the tip of the catheter. The photocell of the electrokymograph was then placed in the beam above the catheter and approximately 2 mm from its tip. On the injection of Urokon 70 %, the contrast jet passed through the roentgen beam causing a decrease in the amount of roentgen rays striking the photocell. Fig. 2 shows a comparison between the electric indication

made by the syringe microswitches in the electrocardiographic circuit and the corresponding response of the electrokymographic photocell. Catheters of caliber varying from Nos. 8 to 11, all 100 cm in length, and 25 ml Urokon 70 % were used. The last curve represents the injection through a brass tubing of the same length, but with an internal diameter corresponding to a catheter of No. 8.5. The electric and electrokymographic indications of the beginning and end of injection do not completely coincide, but are within limits considered acceptable for this study; the discrepancy is probably chiefly due to the difficulty in the exact adjustment of the mechanical microswitches. The main features of the densographic recordings are essentially the same in all tracings. The deflection of the curve, of course, is more pronounced when a larger catheter is used. The type of the densographic recording found when contrast material is injected through the brass tubing does not seem to differ from that obtained by injection through the cardiac catheters.

Results

1. Injection of physiologic saline solution or Urokon into the right atrium did not change the atrial pressure to any large extent. The normal respiratory pressure variation in the right atrium was generally more prominent than the pressure change produced by the injection (Fig. 3). An irregular increase in the atrial pressure of approximately 1 to 2 mm Hg was generally found during the next few heart beats.

2. The pressure effects in the right atrium on injection of physiologic saline or Urokon into the inferior vena cava at the level of the renal or hepatic veins gave roughly the same pressure effects as direct injection into the right atrium (Fig. 4).

3. When injection and pressure measurements were made in the right ventricle, extrasystoles occurred more frequently than with injection into the right atrium. As might be expected, a somewhat more pronounced effect was found on the ventricular pressure as compared with the atrial pressure changes (Fig. 5). The systolic pressure was continuously raised during 2 to 7 heart beats following the injection of saline. The pressure then gradually returned to its original level after another 2 to 7 heart beats. The maximum rise in systolic pressure was generally 20 to 30 per cent of its original level. Synchronously with the rise in systolic pressure, a slight decrease in the ventricular diastolic pressure was found. On injection of Urokon, the same type of pressure change was found, but to a lesser degree.

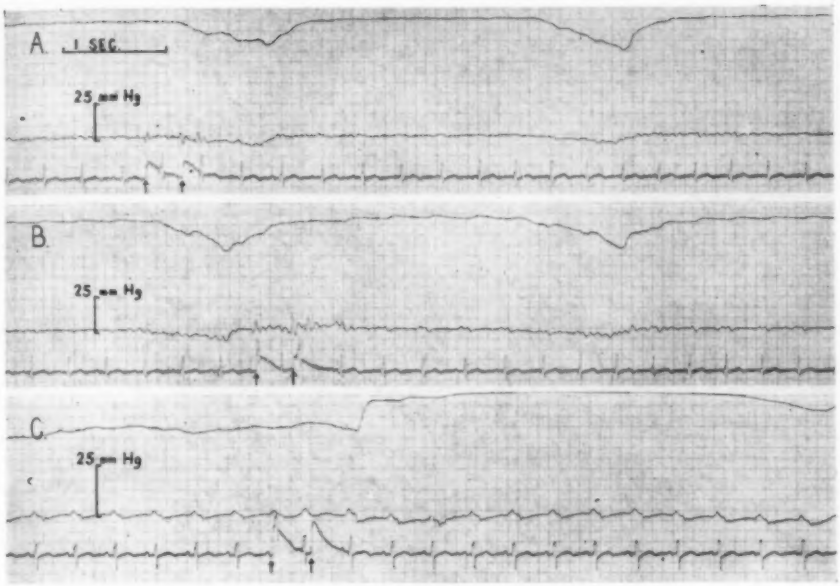

Fig. 3. Pressure effect in right atrium on injection of 1 ml of physiol. sal. sol. per kg body weight (A and B), and Urokon 70 % (C). Top curve in each recording is a densometric tracing of respiration. Beginning and end of injection are indicated on electrocardiogram.

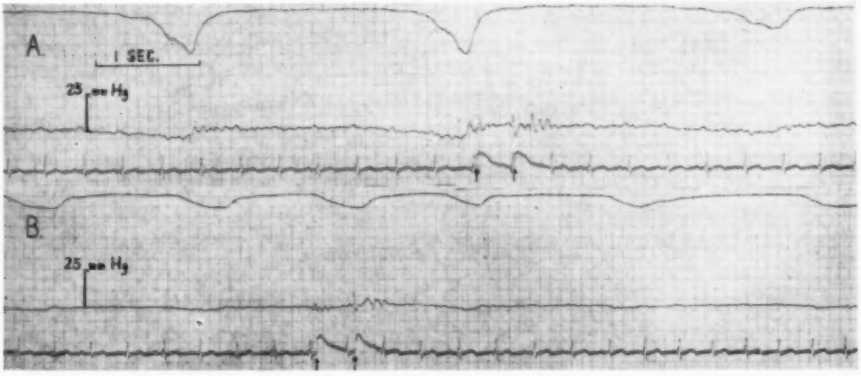

Fig. 4. Pressure effect in right atrium by injection of 1 ml of physiol. sal. sol. per kg body weight into inferior vena cava at level of hepatic veins (A) and renal veins (B). Approximately the same pressure change is obtained in right atrium as by injection directly into it (cf. Fig. 3).

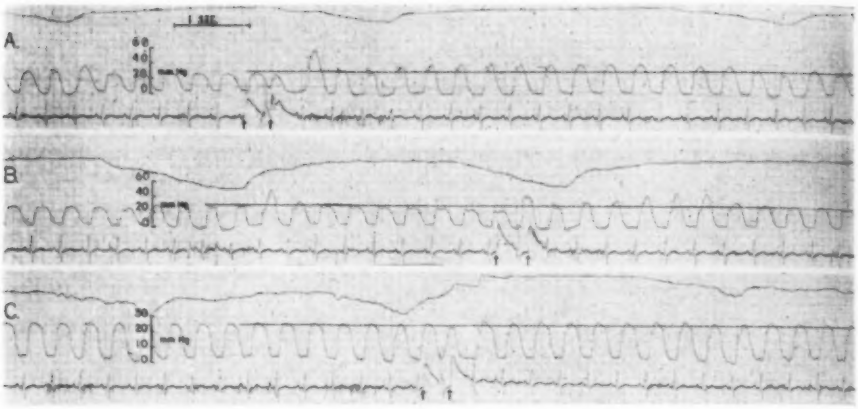

Fig. 5. Pressure effect in right ventricle by injection of 1 ml of physiol. sal. sol. per kg body weight (A and B) and Urokon 70 % (C) into right ventricle; moderate pressure rise occurs during several heart beats in conjunction with the injections, an effect more prominent after injection of saline than when contrast material is used.

Discussion

The increase in atrial pressure on injection of saline or Urokon into the atrium or inferior vena cava is fairly small in spite of the volume injected and the short injection time. An explanation for this may be that the venae cavae and the liver veins can act as pressure reducers by collecting part of the increased volume of fluid produced by the injection. The basic conditions in the normal dog seem, in any case, not to be favorable for the production of high pressure during the procedure of selective angiocardiography when the contrast material is injected into the right atrium. In addition, the injection time in the usual selective angiocardiography is three to five times longer than that used in the present study.

The pressure changes produced by injection into the right ventricle have been moderate. It is possible, however, that the systolic pressure rise at the end of the injections would have been higher if smaller catheters had been used or if only the injection catheter had been introduced in the ventricle. There is a definite possibility that insufficiency of the tricuspid valve may be produced by introducing two catheters, or even one catheter, of No. 10 size; part of the fluid injected under these conditions could have escaped back into the right atrium. At the same time, however, we must consider that a pressure rise in the right ven-

tricle greater than the pulmonary arterial pressure may open the pulmonary valve. The lungs also have a considerable capacity for changing their volume of contained blood without altering the pulmonary vascular resistance. With a rapid fluid injection into the right ventricle, the pulmonary vessels will probably serve to reduce the pressure in the right ventricle.

Under pathologic conditions, *e. g.* in cases with increased resistance in the pulmonary vessels, more pronounced elevation of atrial or ventricular pressure may reasonably be expected to occur with rapid injections into the right heart.

This investigation was carried out during the tenure of a James Picker Foundation Fellowship in Radiologic Research.

SUMMARY

The effect on the pressures in the chambers of the right heart of rapid injection of saline and Urokon 70 % through a selectively placed catheter was studied in 10 dogs. The technique employed is described and the significance of the pressure changes recorded discussed.

ZUSAMMENFASSUNG

Der Einfluss einer sehr schnellen Injektion einer Salzlösung und 70 %igem Urokon durch einen selektiv plazierten Katheter auf die Druckverhältnisse in den Kammern der rechten Herzhälfte wurde an 10 Hunden studiert. Die dabei benutzte Technik wird beschrieben und die Bedeutung der registrierten Druckveränderungen wird diskutiert.

RÉSUMÉ

L'auteur a étudié sur 10 chiens l'effet de l'injection rapide de sérum salé et d'Urokon à 70 % par un cathéter placé sélectivement sur les pressions dans les cavités du cœur droit. Il décrit la technique utilisée et examine l'importance des modifications de pression enregistrées.

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ANGIOCARDIOGRAPHY IN MITRAL DISEASE

Preliminary report

by

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In 1939 ROBB & STEINBERG reported the first successful venous angiocardiographic examinations in adults. With the aid of angiocardiography, these authors could observe typical changes in the size and shape of the heart chambers in mitral disease. Similar studies were reported by GRISHMAN et coll. in 1944. ZINSSER et coll. used angiocardiography in a great number of cases of mitral disease. Their technique was essentially the same as that of ROBB & STEINBERG, namely, venous injection of the contrast medium and a small number of exposures in one projection (the antero-posterior); they used no general anesthesia. ZINSSER et coll. analyzed the shape and size of the different chambers of the heart, and in addition studied alterations in the circulatory dynamics accompanying mitral disease as reflected in the circulation velocity of the contrast solution injected. Thus, these authors reported a more rapid circulation through the heart in mitral insufficiency than in stenosis.

All these investigators used for the most part single-plane examinations and relatively few exposures with an exposure frequency of up to 1 exposure per second. Furthermore, they did not take any measures for the purpose of determining the position of the exposures in relation to the different parts of the heart cycle such as, for instance, a simultaneous electrocardiogram (ECG) and automatic exposure tracing. This would, however, seem to be essential for hemodynamic studies in angiocardiography (WESTERMARK, WEGELIUS & LIND, KJELLBERG et coll., and others).

BIÖRCK, AXÉN et coll. were the first to use exposure markings on the ECG during angiocardiographic investigations in mitral disease. They exposed films in two perpendicular planes with an exposure rate of 2

Submitted for publication 28 May 1956.

per second. With the aid of this technique they were able to observe volume variations of the left atrium and ventricle during the heart cycle in mitral disease. This method thus seems likely to prove helpful in hemodynamic studies. Two exposures per second must, however, be regarded as too low a film frequency for a more detailed circulatory study of the heart (WEGELIUS & LIND).

BJÖRK, KJELLBERG et coll. used direct puncture of the left atrium, injecting contrast medium directly into that chamber. For their angiocardiographic examinations they used one projection with the central ray parallel to the left atrio-ventricular septum, which permitted roentgen-anatomic studies of the actual mitral ostium and valves.

SOLOFF et coll., using a biplane, stereoscopic angiocardiographic apparatus with simultaneous recording of the carotid pulse, studied normal individuals and cases of mitral stenosis with the aid of venous angiocardiography. They placed great importance on impairment of the intra-cardiac circulation time. The duration and degree of opacification of the heart chambers in mitral stenosis was also given much attention. These authors endeavoured also to determine the volume of the left atrium from the appearance of the angiocardiograms.

Personal investigations

Method. JÖNSSON, BRODÉN & KARNELL (1949) discussed the general methods of angiocardiography and emphasized the selective principle of injection, claiming that for the demonstration of the left side of the heart, injection into the pulmonary artery was the method of choice. At that time, however, the technical equipment was not satisfactory. Thus, JÖNSSON (1953), in a survey based on experiences up to 1951, stated that the methods for visualization of the left side of the heart were still not satisfactory but that the most distinct opacification was obtained by injecting into the pulmonary artery. Owing to subsequent developments, in particular in the technical equipment, it has been possible to improve the method described by JÖNSSON et coll. to such an extent that it is now always possible to obtain adequate opacification of the left side of the heart in mitral disease. With the hemodynamic investigation in mind, a technique has been worked out on the following principles.

1. A two-plane film changer is used, with which it is possible to expose 6 pairs of pictures per second. In most of the examinations, the type I film changer described by GIDLUND (1956) was used. For this, a high output generator permitting short exposure times (max. 0.06 sec) together with high loading is necessary. This arrangement gives clear-

cut pictures plainly showing the opacified parts of the heart. The Elema Triplex Automatic, 150 kVp, 1000 mA apparatus, is used for the purpose.

2. A large amount of contrast medium, 1.2 to 1.5 ml of iodopyracet 70 % or sodium acetrizoate 50 % per kilogram of body weight, is injected into the pulmonary artery at a rate of 20 to 25 ml/sec. The contrast material is injected through a cardiac catheter with its tip in the pulmonary artery. The injection is achieved by an automatic pressure syringe. The apparatus designed by GIDLUND for this purpose was used in all the examinations.

3. General anesthesia should be used, aiming at producing the clearest possible opacification of the left heart and standardizing the conditions for the examination.

4. The different exposures made during the angiocardiographic examination are recorded simultaneously with an electrocardiogram.

In practice, the examination was carried out along the following lines:

Immediately after right heart catheterization, including pressure measurements, the catheter is positioned for the injection of contrast medium, with its tip in the pulmonary trunk. The patient is always examined under general anesthesia, not only for his consideration but also because it is much more easy to obtain standardized conditions during the examination. A combination anesthesia is used, consisting of meperidine, pentothal sodium, succinylcholine (= celocurine, a short-acting synthetic preparation with curare-effect) and oxygen (EYRICH). The patient is intubated for control of respiration. Intubation furthermore reduces radiation hazards for the anesthetist. Standing outside the examination room, he can inflate the patient during the exposures by means of a rubber tubing connecting the tracheal tube with the anesthetic machine. When the action of the celocurine has reached its maximum, the contrast solution is injected. The high injection speed makes it necessary to use a relatively wide catheter (F 10 to F 12), since the jet from a narrower catheter has a cutting effect. This may be dangerous, especially if the catheter, in connection with the injection, recoils to the infundibulum, where the wall is easily damaged. Possibly, a safer solution to this problem is a side-hole catheter. A catheter of this kind has been tried at a few examinations, but our experience with it is too limited to permit any definite estimation of its value.

The film changer may be started at any moment desired, during the injection. The exposure procedure commences when about 20 ml of the contrast medium remains in the pressure syringe, *i. e.* when there is an adequate concentration of contrast material in the pulmonary artery for the first films.

The film changer is equipped with a program selector with possibilities for arranging three different series of exposure rates. Our aim in mitral disease examinations is to demonstrate roentgenologically both the pulmonary vessels and the passage of the contrast medium through the left side of the heart and aorta. This is achieved with a minimum of exposures when the following program is adopted.

1. Three exp./sec for 2 seconds with the start towards the end of the contrast injection. During this phase the pulmonary artery and its branches are visualized.

2. A pause of 2 to 3 seconds, during which the contrast material passes the pulmonary capillaries. This pause is justified by the fact that, from the angiocardiographic point of view, nothing of interest is seen during this phase.

3. Six exp./sec for 5 to 6 seconds, for the demonstration of the pulmonary veins, left atrium, left ventricle and aorta (Phase 3).

The anesthetist adapts his technique to the exposure program in the following way: Immediately before the injection is started, the anesthetist inflates the lungs of the patient with oxygen. The degree of inflation is then diminished and when the lungs are in the medium inspiration position the anesthetist indicates that the injection is to be started. The medium inspiration position is held during the opacification of the pulmonary artery and its branches (Phase 1). During the pause (Phase 2), the anesthetist starts to inflate the lungs to a constant positive pressure of 20 to 25 cm of water. Control of this is obtained by a water manometer connected to the anesthetic machine. This lung inflation is maintained while the contrast medium passes the pulmonary veins, the left side of the heart, and the aorta (Phase 3).

This inflation of the lungs is necessary for three purposes.

1. In order to retard the circulation while the contrast medium is passing the left side of the heart, so as to allow as many pairs of films as possible to be taken of these vascular structures. The lung inflation should, however, not be too high during Phases 1 and 2, because the passage of the contrast material through the lungs may be totally obstructed so that opacification of the left heart and aorta may not be obtained at all.

2. In order to achieve good-quality films. As a result of the lung inflation, the pulmonary tissues, and the opacified vascular structures, come out in clear contrast, while the diaphragm lies at a low level and does not project over the heart.

3. By maintaining a constant intra-thoracic pressure during the passage of the contrast material through the left heart, an element of uncertainty is avoided when the relative volume of the left atrium is determined (cf. p. 106). The volume of this heart chamber depends in fact to some extent on the surrounding pressure, and too forcible inflation may artificially diminish the left atrium.

Immediately after the injection, while the exposures are still in progress, the catheter was in several cases withdrawn. This was done because the catheter was sometimes projected over the mitral valves in the lateral view, disturbing the interpretation of the films. The technique of the examination described does not permit true physiologic studies; it is, however, so standardized that angiocardiographic investigations of the circulatory conditions are rendered possible.

Twenty-five cases of mitral disease were investigated according to the above-described method. There were two complications in the material. In one case bilateral pulmonary edema occurred and in the other the same complication developed in the left lung only. Both patients recovered after treatment. It should be noted that in both cases a highly concentrated (70 %) tri-iodized contrast medium had been used. The left-sided pulmonary edema may, however, have been due partly to the fact that the contrast medium was injected by mistake into the left pulmonary artery only.

Observations

All patients had been diagnosed as having mitral disease before the angiocardiographic examination, and the aim of the latter was chiefly to determine whether an operation should be performed or not. Angiocardiography was always preceded by a thorough clinical investigation including phonocardiography and a heart function test. The investigation also included conventional films of the chest and electrokymography. The results of these investigations will not be discussed in this report. The angiocardiographic findings in the different parts of the lesser circulation and the left heart were as follows.

The pulmonary artery and its branches. STEINER & GOODWIN, among other investigators, have demonstrated the pathologic changes occurring in the pulmonary arteries in mitral disease. The present material demonstrated the same pathologic features as described by these authors. They may be summarized as follows.

1. The central arteries were wider than normal, and in cases with extreme pulmonary hypertension the pulmonary trunk was aneurysmal.

2. At the level of the first division of the pulmonary arteries, a sudden change in the caliber of the arteries occurred. Peripheral to that site the arteries were narrower than normal.

3. The vessels in the peripheral parts of the lungs were tortuous, and there was a striking diminution in the number of arteries peripherally and, above all, at the lung bases.

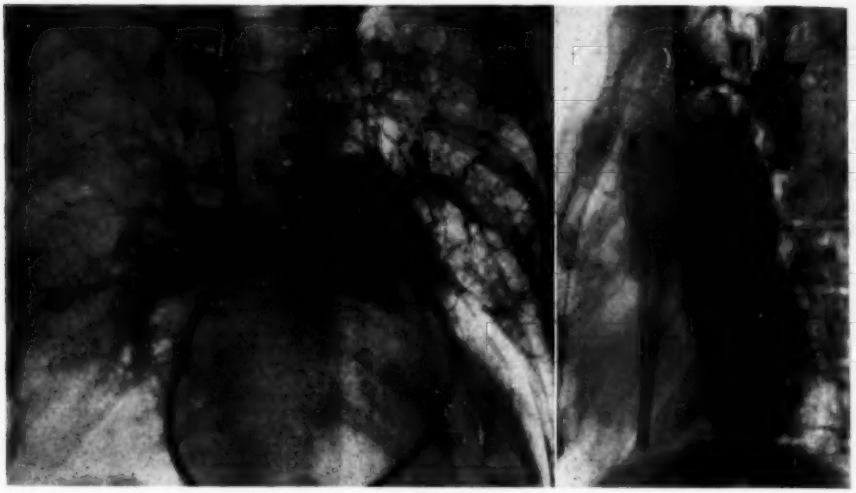
These characteristic findings are demonstrated by Case 1.

Case 1 (Figs. 1 a, b and c). 40-year-old female with a long history of heart insufficiency. Heart: Regular rhythm, no murmur; pulmonary second sound accentuated. B. P. 120/100. Catheterization revealed pulmonary hypertension, 125/87, mean 94, and a PCV pressure of 23 mm Hg. Six months after angiocardiography the patient died, and the autopsy revealed a high degree of mitral stenosis and endocarditis. The left ventricle was normal. There was atheromatosis in the larger pulmonary arteries and intimal thickening and hyalinization in the smaller arteries.

In severe, long-standing pulmonary hypertension, the lung bases seemed to be non-vascular. The pathologic changes described ran approximately parallel to the degree of pulmonary hypertension. These phenomena could also be studied in conventional films and with some experience the pulmonary artery pressure could be roughly estimated.

DEXTER et coll., WOOD, and others make a distinction between active and passive pulmonary hypertension in mitral disease. Active hypertension is said to indicate pulmonary artery congestion, chiefly due to pathologic changes in the arterioles of the lungs, while the passive form is said to be merely the result of venous stasis from the atrium, via the pulmonary veins, to the pulmonary arteries. When the latter is present, the hypertension is of a mild degree. In the present material the findings from angiocardiography and pressure measurements indicated that the two types exist, but in general the distinction between them did not seem to be clear-cut.

In cases with active pulmonary hypertension the increased load on the right heart was manifested by dilatation and hypertrophy of the right ventricle; this caused more or less obvious backward displacement and rotation of the left ventricle. In extreme cases, the normal topography was often considerably disturbed as a result of this anomaly. Strangely enough, the left atrium was only moderately enlarged in these cases.



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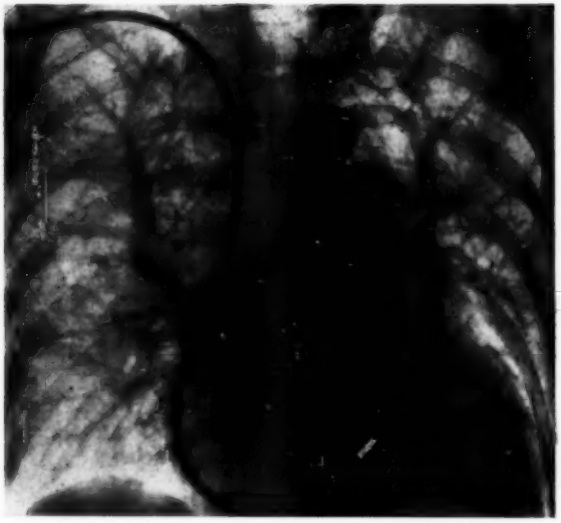


c

Fig. 1. Case 1. Mitral stenosis. Angiocardiography. a) A. p. projection. Pulmonary artery phase. Changes in high degree pulmonary hypertension: Central arteries dilated, sudden change in the caliber of the arteries; non-vascularity of the lung bases. b) Lateral projection in a later phase, when the left side of the heart is opacified. Left ventricle displaced posteriorly by the dilated and hypertrophied right ventricle. c) A. p. projection in the same phase as b. Pulmonary veins tortuous and irregular in size.

The pulmonary veins. The changes in the pulmonary veins in mitral disease are not of the same significance as those in the arteries. The appearance of the veins, however, furnished some valuable information regarding the hemodynamic conditions in mitral disease.

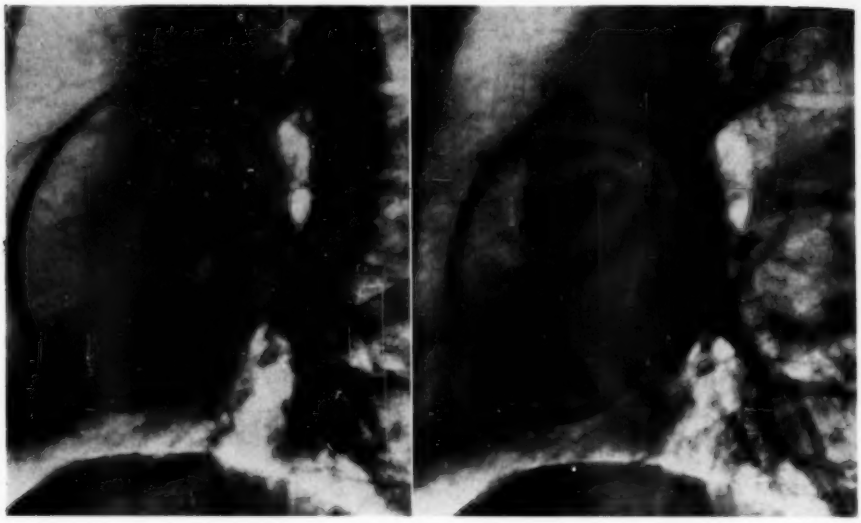
In most instances, there was widening of the central pulmonary veins and this widening could be correlated to the PCV pressure. In cases with a high PCV pressure (30 to 40 mm Hg), the veins were usually tortuous with sudden caliber changes like those in the arteries. When the peripheral arterial vascularization was decreased, the number of veins was also small and their size decreased. No noticeable parallelism between the enlargement of the left atrium and the widening of the pulmonary veins could be established; on the contrary, a striking discrepancy was noted.

The left atrium. The indications for angiocardiography are very limited. Consequently, it was only possible to make an angiocardiographic study of the appearance of the normal left atrium during the heart cycle in a few isolated cases. In those cases without demonstrable cardiac disease that were examined, this heart chamber had in diastole an elliptic shape in the lateral projection, while in atrial systole it decreased concentrically and was almost completely emptied as the atrium reached its maximum contraction.

Case 2 (Figs. 2 a and b). 25-year-old female with no symptoms or signs of heart disease. She had a tumour in the right hilum region, and angiocardiography was made to exclude a vascular abnormity. The contrast injection was made in the pulmonary trunk and revealed no abnormity except for a moderate displacement of the vessels in the vicinity of the tumour.

In mitral disease, however, the behaviour of the left atrium during the heart cycle was different. The increased pressure in the atrium distended its muscular walls. This distention made the shape of the atrium much more regular, so that the atrium projected approximately as an ellipse in both the antero-posterior and the lateral projection ('frontal' and 'lateral ellipse'). On the basis of these findings, volume studies of the left atrium have been made, this heart chamber being treated for the purpose as an ellipsoid ('atrium ellipsoid'). This was possible in mitral disease, because the atrium never emptied as completely as in normal cases, but kept in general its ellipsoid shape during the entire heart cycle. The cyclic alternations in the atrial volume, consequently, were the equivalent of variations in the length of the three axes of the atrium ellipsoid. Of these axes, the transversal axis was more or less fixed in the thoracic cavity by the pulmonary veins, which are closely attached to the atrium on the posterior aspect (KJELLBERG et coll.). The spatial orientation of the atrium ellipsoid axes was, in consequence, to some extent stabilized.

These axes are denoted *a*, *b* and *c* (Figs. 3 and 4). If these axes could be defined in space and then measured, the absolute volume of the atrium could be calculated. The direction of the axis *b* is known in both



a b

Fig. 2. Case 2. Normal subject. Angiocardiography. a) Lateral projection; film exposed during maximum atrial systole. The left atrium is small and it is almost impossible to determine its margin because of the superimposed pulmonary veins. Left ventricle in isometric contraction phase; the aortic valve in opening phase, only the anterior valve being seen. b) Lateral projection; film exposed during atrial diastole. Left atrium considerably larger than in systole and with shape of an ellipse. Left ventricle very near the end of ejection phase but maximum evacuation of ventricle has not yet been reached and aortic valves are still open.

projections and thus defined. The axes a and c are each only recognized in one projection (frontal and lateral projection, respectively), and thus these two axes are not defined geometrically. Two different, arbitrarily chosen possibilities (Alternatives I and II) for the orientation of axes a and c are geometrically analyzed in Fig. 4. (In this discussion no consideration is paid to the geometric magnification.) The absolute volume of the ellipsoid in Alternative I (continuous line) will be:

$$4/3\,\pi\frac{a\,b\,c}{8},$$

and in Alternative II (dotted line):

$$4/3\,\pi\frac{a'\,b\,c'}{8}.$$

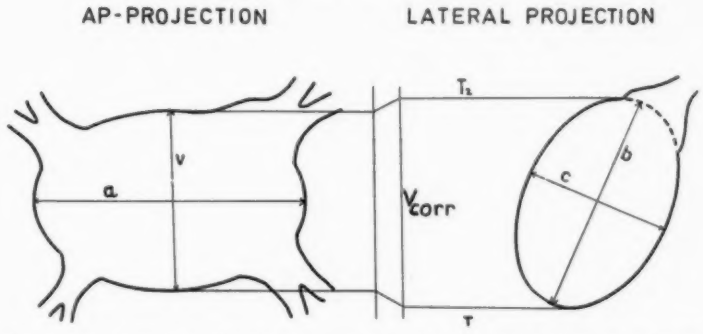


Fig. 3. Schematic drawing illustrating method of calculating relative volume of left atrium.

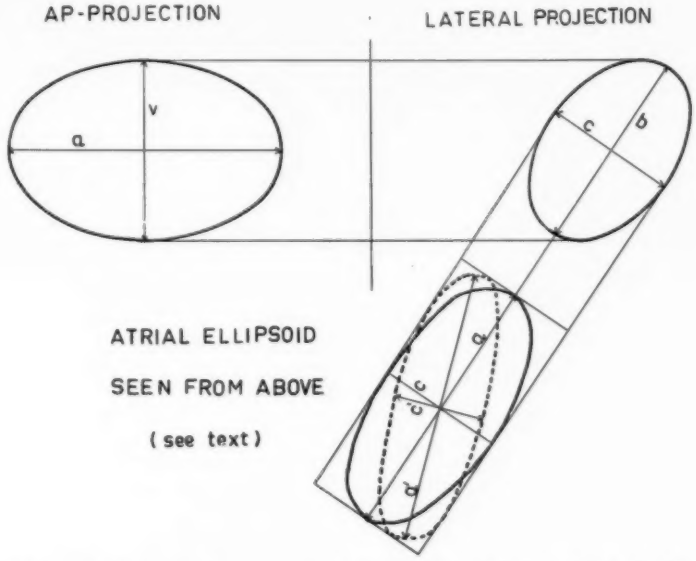


Fig. 4. Schematic drawing to demonstrate that the calculation of the absolute volume of atrium from a. p. and lateral projections is impossible. The orientation of axis *a* in the thoracic cavity is unknown. Two different shapes of the atrium (continuous line = Alt. I, dotted line = Alt. II) are shown, which both give the same volume, calculated from the two projections.

The volume will be different in the two alternatives, but the frontal and lateral projections are exactly the same. The volume of the atrium calculated from the two projections will be

$$4/3\,\pi\frac{a\,b\,c}{8}$$

in both cases. This volume determination is thus only valid if axis *a* is orientated in the true lateral plane as in Alternative I (continuous line). It is proved from this example that it is not justifiable to make absolute measurements of the volume of the left atrium in accordance with the principle outlined above. Axis *a* deviates only moderately from the true lateral plane, because its orientation is more or less maintained by the stabilizing action of the pulmonary veins. Under these circumstances, *a* will vary approximately proportionally to *a'*, and *c* approximately proportionally to *c'* (cf. Alternative II, Fig. 4). Thus, in practice, *a* may represent *a'* and *c* *c'* for the calculation of the relative volume of the atrium. In other words, the product *a b c* will correspond to the relative volume of the atrium. This means that in any phase of the heart cycle, this product will represent the volume of the atrium as compared with the same product in any other phase of the cycle.

Method for measurement of the left atrium. Axis *a* and the measure *v* (*i. e.* the maximum height of the atrium in the frontal projection) are determined in the frontal film. These measures are corrected for the geometric magnification of the film changer. The magnification is 1.2 in the frontal projection. To obtain the real value a_{corr} *a* is thus divided by 1.2. The lower outline of the atrial ellipsoid is well-defined in both projections, but the upper outline is usually only seen in the frontal projection. The upper part of the ellipsoid is often impossible to define in the lateral projection, because of the superimposed pulmonary veins (dotted line in Fig. 3). To be able to construct this invisible part of the lateral ellipse and thus obtain the top of axis *b*, it is necessary to construct the upper tangent to the ellipsoid. This is done by means of the measure v_{corr}. This term is obtained by correcting *v* from the magnification of the frontal projection to that of the lateral projection. In our film changer the magnification in the lateral projection is 1.3 and thus $v_{corr} = v \times 1.3/1.2$. A horizontal tangent, T_1, is drawn through the lower margin of the lateral ellipse. From this tangent the measure v_{corr} is set off perpendicularly. From the top of v_{corr} a perpendicular is constructed, and this represents the top tangent of the ellipsoid (T_2). With the aid of this tangent the upper part of the ellipsoid is constructed and it is then possible to obtain the measures *b* and *c* from the lateral film. *b* and *c* are corrected for the geometric magnification of the lateral plane; the corrected values are thus $b_{corr} = b/1.3$ and $c_{corr} = c/1.3$. a_{corr} has been determined earlier. Since there is no point in keeping the constants of the volume determination we have used the product $a_{corr} \times b_{corr} \times c_{corr}$ as a measure of the relative volume of the atrium.

This was determined according to the described method in all films with adequate opacification of the atrium. The timing of the exposure in the heart cycle for each pair of films was obtained from simultaneous ECG and exposure recordings. As a result of these measures, the relative atrial volumes from different phases of the cardiac cycle could be compared with one another and the volume variations in the atrium during the cardiac cycle could be studied.

In practice, the values for the relative atrial volume were plotted against the ECG. Those values in which the atrial volume had decreased as a result of too pronounced inflation of the lungs (cf. p. 100) were, however, excluded from the calculations. All reliable volume measurements from one case were put in just one heart cycle and that cycle was repeated in order to clearly demonstrate the tendency of the values. In 10 cases, a sufficient number of measurable film pairs were obtained to make it worth while compiling the relative volume determinations into a curve (volume-quotient curve to be

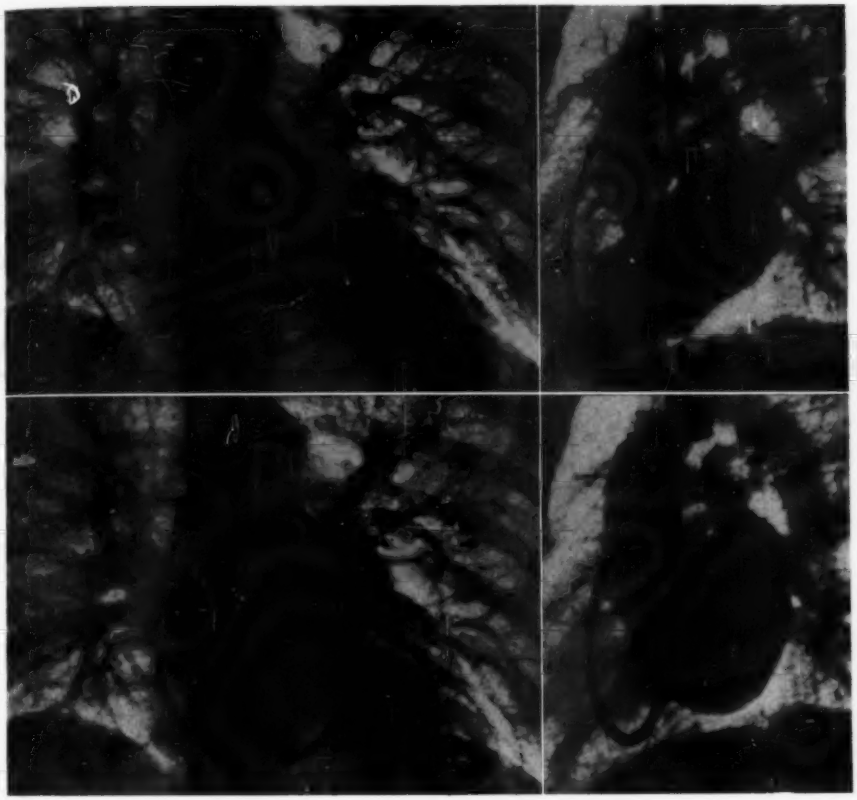


Fig. 5. Case 3. Mitral stenosis and arterial hypertension. Angiocardiography. a) A. p. projection. Atrial systole. Note shape of left ventricle and thickness of left ventricular wall, best seen in the region of apex. b) Lateral projection. Atrial systole. Aortic valves not well visualized in this case but there is no poststenotic dilatation of ascending aorta. c) A. p. projection. Ventricular systole. Left atrium considerably larger than in *a*. Left ventricle has emptied almost completely. d) Lateral projection. Ventricular systole. The almost complete evacuation of the left ventricle is evident.

called VQC in the remainder of this paper). This curve thus showed in detail the cyclic volume variations of the atrium.

In 15 cases, films with adequate opacification of the atrium were too few to justify the making of a curve. It was, however, possible to make measurements, in one pair of films in maximum atrial contraction, and one pair in the beginning of diastole, representing the minimum volume (Vol_{min}) and the maximum volume (Vol_{max}), respectively, of the atrium. From these two relative volume determinations the quotient Vol_{max}/Vol_{min} (volume quotient, to be called VQ in this paper) was obtained. Quotients such as

$$\frac{Vol_{max} - Vol_{min}}{Vol_{max} + Vol_{min}}; \quad \frac{Vol_{max} - Vol_{min}}{Vol_{max}} \text{ and } \frac{Vol_{max} - Vol_{min}}{Vol_{min}}$$

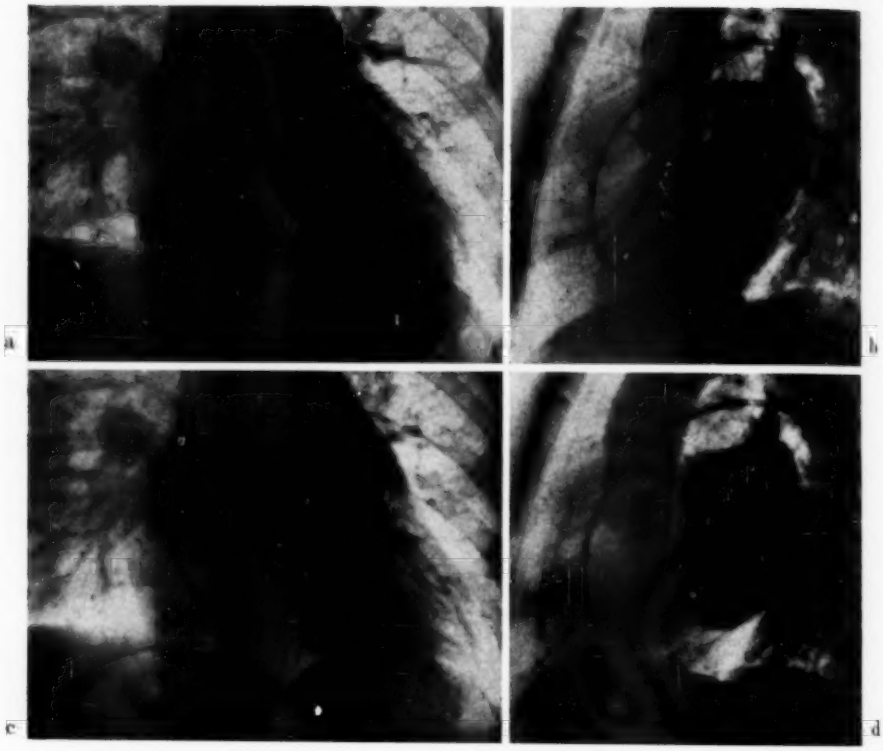


Fig. 6. Case 4. Mitral insufficiency. Angiocardiography. a) A. p. projection. Atrial systole. Left atrium is small but left ventricle enormously dilated. b) Lateral projection. Atrial systole. c) A. p. projection. Ventricular systole. Film exposed during maximum ventricular contraction and there is still blood in sinus part of ventricle. d) Lateral projection. Ventricular systole.

were also determined. In addition, the difference between the maximum and minimum of the atrium ellipsoid was calculated without reference to the spatial orientation of the axes of the ellipsoid. The VQ proved to be the most reliable of these mathematical calculations for studying volume variations in mitral disease. In the cases investigated, its value varied between 1.0 and 2.5. The variations in the VQ seem to be approximately correlated to certain hemodynamic changes in the left atrium. However, if the atrium is greatly dilated, caution should be exercised in basing conclusions on the VQ, since, in these cases, uncertain values can be expected owing to the fact that the quotient between equivalent absolute volume variations will be smaller in large atriums than in small ones.

It should also be pointed out in this connection that the method for measuring the relative left atrial volume cannot be regarded as a true mathematical one. Certain objections can be raised against it, among others as regards the analysis by solid geometry as such, and relevant facts such as the atrium not being an absolutely regular ellipsoid

and that its borderline is sometimes rather ill-defined. For practical purposes, however, the method has proved valuable for the interpretation of angiocardiograms in mitral disease.

The left ventricle. The irregular shape of the left ventricle rules out the possibility of volume studies in accordance with the afore-mentioned principles. It was, however, possible to make an approximate estimation of the ventricular volume variations from both the antero-posterior and the lateral projections. In normal cases, the left ventricle emptied almost completely, *i. e.* the residual amount of blood during maximum ventricular contraction (ventricular residual blood, to be called VRB in this paper) consisted merely of a small residue beneath the aortic valves (Figs. 5 b and d). Certain hemodynamic alterations, however, seem capable of causing an increased VRB. The degree of VRB was therefore divided into two groups: 1) the normal VRB, where a very small residual amount of contrast medium was seen under the aortic valves (Figs. 5 b and d), and 2) the pathologic VRB, where contrast medium was seen also in the sinus part of the ventricle during maximum ventricular contraction (Figs. 6 b and d).

A flow of contrast medium through the mitral ostium was often observed during ventricular diastole. This was only evident in the lateral projection. In consequence, it was only possible to form a vague idea of the appearance of the actual ostium, and it was not possible to estimate its cross-section area. The papillary muscles could, however, be distinguished in lateral projections. The thickness of the ventricular wall could be estimated in most cases. Measurements of the wall were made in the apex region, where the outer contour of the wall was clearly visible in frontal films obtained in diastole. Along these lines, the thickness of the wall was determined as being between 6 and 12 mm.

The aortic valves were often seen in the lateral projection sufficiently clearly to enable us to judge their thickness and to follow their movements during the cardiac cycle. The ascending aorta was also distinctly opacified, and we were able to form an idea of its caliber and configuration.

Results

Observations in cases of uncomplicated mitral stenosis. Fourteen cases in the material were considered to be uncomplicated mitral stenosis. Of these, 13 had regular rhythm. In all the cases the clinical, roentgenologic, and electrokymographic findings indicated a typical stenosis.

In the mitral stenosis group the pulmonary arteries were always more or less pathologically changed in the manner described earlier (cf. p. 101). There was a striking correlation between the degree of pulmonary hypertension and the changes in the arteries. There was always more or less pronounced dilatation of the left atrium in the cases of uncomplicated mitral stenosis. The degree of dilatation could not, however, be correlated either with the pulmonary artery pressure, or the PCV pressure. There was always a significant amount of residual blood in the atrium during its maximum contraction.

The VQ value in the cases with sinus rhythm was between 1.2 and 1.5, thus within a narrow range. In the case with auricular fibrillation the VQ was 1.0; in other words, no volume variations could be registered during the heart cycle.

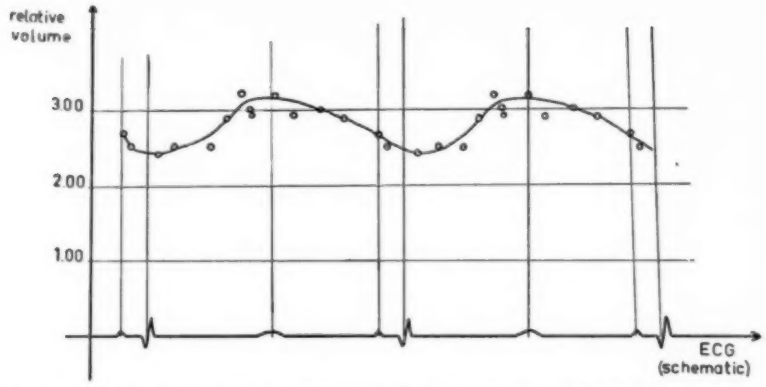


Diagram 1. Volume variations of left atrium during heart cycle (VQC) in pure mitral stenosis. Relative volumes of atrium plotted against the ECG. Both the emptying and filling of the left atrium are relatively slow. The maximum volume is close to the T-wave, and the minimum volume immediately after the QRS complex.

The typical features of the VQC in mitral stenosis (cf. Diagram 1) were found to be a slow volume increase during the ventricular ejection phase. The volume maximum occurred near the end of the T-wave of the ECG. Thereupon followed a successive decrease in volume during the ventricular diastolic phase, which ended with the volume minimum immediately after the QRS-complex of the ECG. In diastole, the left ventricle was never dilated, but was, if anything, smaller than normal. In most cases the ventricle emptied almost completely, and the VRB was thus normal. Four cases of clinically pure mitral stenosis, however, had a pathologic VRB with contrast material in the sinus part of the ventricle during maximum contraction. In these four cases a concomitant lesion must be suspected. The thickness of the ventricular wall was 6 to 8 mm in the majority of the mitral stenosis patients. In two of the four last-mentioned cases with a pathologic VRB, however, the wall was 9 and 12 mm thick, respectively.

Case 3 (Figs. 5 a—d). Mitral stenosis. 32-year-old female with a history of rheumatic disease, and dyspnea and palpitations for the previous five years. Heart: Regular rhythm; short presystolic murmur heard at the apex; no systolic murmur. B. P. 190/90. Heart catheterization revealed moderate pulmonary hypertension, 35/22 mm Hg, mean 29 mm. PCV pressure 29 mm. Angiocardiography showed caliber changes in the pulmonary arteries. The pulmonary veins were slightly wider than normal and the left atrium was dilated. VQ = 1.4. The left ventricle was practically normal in size and emptied almost completely. The left ventricular wall was much thicker than in uncomplicated mitral stenosis (12 mm in diastole). This hypertrophy can be explained by the arterial hypertension.

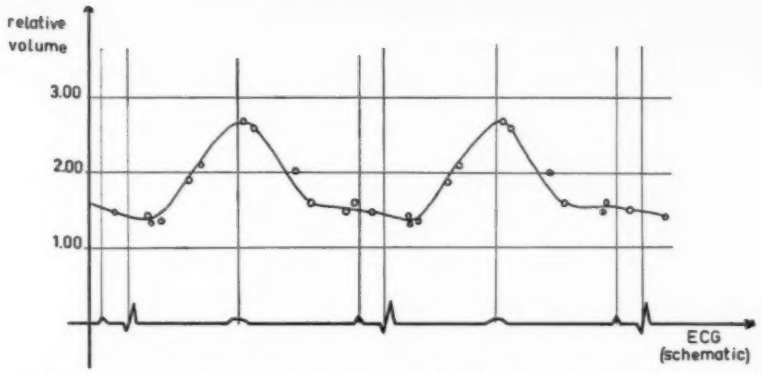


Diagram 2. Volume variations of left atrium during heart cycle (VQC) in predominant mitral insufficiency. Relative volumes of atrium are plotted against the ECG. Note rapid volume increase during maximum systolic ejection of left ventricle and the rapid decrease during rapid filling phase of left ventricle. Maximum volume is near the T-wave and minimum volume immediately after the QRS-complex.

Observations in cases interpreted as predominant mitral insufficiency. From every point of view, it is much more difficult to define mitral incompetence than mitral stenosis. Mitral insufficiency is a patho-physiologic concept. The pathologist can estimate the cross-section area of the valve and observe the conditions in the valve leaflets, but cannot form any correct idea of the hemodynamic alterations. For the cardiac surgeon too, it is very intricate to estimate the degree of incompetence in the mitral ostium; if his finger feels a regurgitating jet of blood during valvulotomy, he knows that there is an insufficiency, but it is impossible to make a quantitative estimation of the amount of blood which is regurgitated to the left atrium. A small jet with a high velocity is much more palpable than a thick one with low velocity (BROCK).

Our material comprises 4 cases which were considered to have predominant mitral insufficiency. In all cases except one, this diagnosis was made before the angiocardiography. None of these patients was operated on, since the operative methods for correcting mitral incompetence cannot yet be considered safe.

Our angiocardiographic observations in mitral insufficiency can be summarized as follows.

The pulmonary arteries were normal or only slightly dilated centrally, as in mild cases of mitral stenosis. On the other hand, changes in the pulmonary veins were clearly visible in all cases (cf. p. 102). The left atrium was dilated in all cases; in one case with atrial fibrillation it was extremely large. In none of the cases of mitral incompetence was a

regurgitant jet through the atrio-ventricular ostium observed angiocardiographically. The opacification of the left atrium took place very rapidly in the present material. This finding has also been described by ZINSSER et coll. The cyclic volume variations of the left atrium were considerably greater among the cases with mitral insufficiency than in those with stenosis.

The VQ in the mitral incompetence cases with regular rhythm was 2.0—2.4, and thus was much larger than in cases of pure mitral stenosis. One case of suspected mitral incompetence with atrial fibrillation had a VQ of 1.3.

The VQC in predominant mitral insufficiency (Diagram 2) diverged from that of mitral stenosis inasmuch as there was a strikingly rapid volume increase, starting approximately simultaneously with the rapid ejection phase of the ventricle (WIGGERS). This volume increase continued approximately to the end of the T-wave of the ECG. The volume maximum and minimum occurred in roughly the same phases of the heart cycle in both mitral stenosis and insufficiency.

In the four cases of mitral insufficiency, the left ventricle was more or less dilated with a pathologic VRB in every instance (Figs. 6 b and d). The thickness of the ventricular wall was measured as 8 to 12 mm. Thus, the wall was thicker in the mitral insufficiency cases than in the stenosis cases.

Case 4 (Figs. 6 a—d). Predominant mitral insufficiency. 33-year-old female with a history of rheumatic fever. Dyspnea during the past ten years. Heart: Regular rhythm, a loud systolic murmur was heard over the apex, no diastolic murmur. B. P. 120/80. Heart catheterization showed mild pulmonary hypertension, 28/14 mm in the pulmonary artery, no PCV recordings could be obtained. Angiocardiography: The pulmonary arteries were not demonstrated, the pulmonary veins were a little wider than normal. Considerable enlargement of the left atrium with enormous volume variations. VQ = 2.2. The left ventricle was dilated and the residual blood in maximum ventricular systole was obvious. The aortic valves were normal and there was no poststenotic dilatation of the ascending aorta.

In addition to the cases with clinically defined mitral stenosis or incompetence, five cases diagnosed clinically as mitral stenosis were examined. They had a VQ of between 1.5 and 1.7, however, in other words, higher than in the pure mitral stenosis cases. A pathologic VRB was also present in all of them.

The possibilities for diagnosing complicating aortic valve disease. One case of combined mitral stenosis and aortic insufficiency and one of mitral and aortic stenosis were observed. The aortic valve lesions were diagnosed by thoracic aortography (CASTENFORS et coll.; FALHOLT et coll.). In the case with aortic stenosis, the aortic valves were rigid, and a narrow jet of blood could be seen in the opacified ascending aorta

during the ventricular systole. Angiocardiography of the same case showed altered action of the aortic valves, and a poststenotic dilatation of the ascending aorta. These observations indicate that a complicating aortic stenosis can be diagnosed angiocardiographically in some cases at least. In the case with aortic insufficiency the thoracic aortography showed regurgitation of contrast solution to the left ventricle. Angiocardiographically, the pattern of mitral stenosis was found, except that there was a considerably pathologic VRB and that the ventricular wall was thicker than it usually is in mitral stenosis, in that it measured 10 and 13 mm, respectively.

Discussion

The great number of different methods developed for the differential diagnosis between mitral stenosis and mitral insufficiency show clearly the difficulty of this problem. Several investigators have shown the usefulness of angiocardiography as a complement to clinical investigation and pressure measurements.

Three types of angiocardiography have been mainly used, differing with regard to the site selected for injection of the contrast solution, *viz.*:

1) Venous angiocardiography
2) Angiocardiography with injection into the left atrium
3) Angiocardiography with injection into the pulmonary artery.

The venous injection technique as evolved by Robb & Steinberg gives a survey of the anatomy of the right heart and lung vessels. The left side of the heart, however, is often difficult to interpret, because contrast material in the right heart and intrathoracic vessels is superimposed. The long distance between the site of injection and the left side of the heart makes the opacification of the latter unsatisfactory.

Apart from anatomic studies, Zinsser et coll. and Soloff et coll. used venous angiocardiography for investigating the circulation velocity of the contrast solution. Without a strictly standardized technique the results of such an investigation must be very unreliable.

The method of Björk, Kjellberg et coll., with injection of the contrast medium directly into the left atrium, is selective in the true sense of the word, *i. e.* the contrast medium is injected as close as possible to the diseased part of the heart, the mitral ostium. We have had no experience of this technique. With the special projection for demonstration of the mitral ostium, only one film plane is used, and thus it is impossible to make three-dimensional studies of the heart chambers. Furthermore, the exact size and shape of the mitral ostium is impossible to determine from only one projection. Owing to the direct puncture of

the left atrium, the method makes it possible to measure the pressures in the left atrium, left ventricle, and aorta. BAGGER et coll. report, however, more or less severe complications in up to 20 per cent of the cases when angiocardiography is performed.

Both in venous angiocardiography and in angiocardiography with injection of the contrast medium into the left atrium, special catheterization of the right side of the heart must be carried out if the pressure conditions in this part of the heart are to be investigated. With the present method, on the other hand, right heart catheterization is performed in connection with angiocardiography. The catheter is introduced into the right side of the heart, where pressure measurements are first made, and samples taken for oxygen analysis. When this has been done, the catheter tip is placed in the pulmonary trunk and in this position contrast medium is injected through the catheter. This angiocardiographic examination makes possible a detailed study of the arteries and veins of the lungs. Anatomic alterations as well as hemodynamic changes in the left side of the heart may be evaluated. We have paid special attention to the volume variations of the left atrium during the heart cycle, and a method for objective evaluation of the volume changes has been developed (ARVIDSSON). Results of diagnostic importance have been obtained from this study. The complications are few and not of a serious character.

The results with regard to the alterations in the lung arteries are in good agreement with the findings of earlier investigations (STEINER & GOODWIN, ACTIS DATO et coll., and others). Like FLEISCHNER & SEGALL, and other authors, we have found that the alterations in the pulmonary arteries can be diagnosed in conventional chest films.

In connection with extreme pulmonary hypertension the right heart may be greatly dilated and hypertrophied, resulting in backward displacement of the relatively small left ventricle. The same phenomenon occurs more or less in certain types of congenital heart disease. The changes may be so pronounced as to cause differential diagnostic difficulties. This is demonstrated by Case 1, in which there was enormous dilatation of the right ventricle but only moderate enlargement of the left atrium. This discrepancy may be explained by the extremely high PA pressure and the relatively lower PCV pressure. Thus, the main pressure fall was in the pulmonary arterioles and capillaries. This pressure barrier in the pulmonary circulation counteracts the dilatation of the left atrium that usually occurs in high-degree mitral stenosis.

In cases of predominant mitral insufficiency there were relatively small changes in the pulmonary arteries, owing to the low pulmonary artery pressure (BURCHELL & EDWARDS). On the other hand, there were marked structural changes in the pulmonary veins of the same type as

in the cases of mitral stenosis. In mitral insufficiency, the left atrium was sometimes considerably dilated as compared with the pulmonary veins, but in other cases the atrium was only moderately dilated, while the central pulmonary veins were much wider than normal, and the latter seemed to replace the left atrium as a blood depot. The degree of dilatation of the left atrium thus does not seem to have any significance from the differential diagnostic point of view as regards mitral stenosis versus insufficiency. Thus, we have not been able to confirm the observations of STEINER & GOODWIN.

On a theoretical and practical basis, we found it impossible to determine the absolute volume of the left atrium with the method described. SOLOFF et coll. tried to determine the absolute volume of the atrium, but they did not discuss the mathematic and practical problems of the method, nor its reliability. Furthermore, they did not mention in what phase of the heart cycle they made their determinations. They claim that the volume of the left atrium was "twice to twelve times the normal" in spite of the fact that they only succeeded in obtaining a value for the volume in one normal case. These authors claim that "in mitral stenosis the left atrium undergoes relatively little cyclic changes in size". Other authors such as BIÖRCK, AXÉN et coll. have observed cyclic volume variations of the left atrium in mitral disease, especially in insufficiency.

There is no objective method described in the literature for the determination of the relative volume of the left atrium. The present method permits observations of the cyclic volume changes of the left atrium. The findings are in agreement with the conceptions of the hemodynamics in mitral stenosis and insufficiency.

In mitral stenosis the minute and stroke volumes are smaller than normal (ELIASCH, and others) owing to faulty evacuation of the left atrium. Thus, a relatively small amount of blood passes from the left atrium to the ventricle. Presuming that no shunting or regurgitation to the atrium occurs, the volume variations of the atrium will be small. In full agreement with this reasoning, we found relatively small volume variations in cases of mitral stenosis (a low VQ as compared with the VQ values in cases of mitral insufficiency).

In cases with predominant insufficiency the alterations of the hemodynamic patterns are different. There is no difficulty in the emptying of the left atrium, but during and immediately after the ventricular systole blood is regurgitated to the left atrium from the ventricle (WIGGERS & FEIL). In other words, in the phase in which, under ordinary circumstances, the atrial volume is at its greatest, an extra amount of blood comes into the atrium (WIGGERS & FEIL). This means that the maximum volume of the left atrium will be relatively great compared to the minimum volume, *i. e.* the VQ value will be high.

Angiocardiographic studies of the left ventricle with special reference to its appearance during different phases of the heart cycle are sparse in the literature. CHAVEZ et coll. maintain that under normal circulatory conditions the left ventricle empties completely in systole; this does not occur, on the other hand, in certain forms of circulatory disturbance. KJELLBERG et coll. describe the cyclic variations of the size and shape of the left ventricle, and point out that its mode of contraction is different from that of the right ventricle. SOLOFF et coll. claim that the left ventricle empties "almost completely" in systole "unless failure is present".

According to the present investigation, in pure uncomplicated mitral stenosis there is only contrast material in the conus beneath the aortic valves during maximum ventricular contraction. If there is also contrast substance in the sinus part of the ventricle this is an indication of alteration in the hemodynamics of the left ventricle. This must be looked upon as an angiocardiographic demonstration of the increased amount of residual blood in the left ventricle. The causes for increased residual blood may be numerous (NYLIN, FRIEDMAN). In our material we found increased VRB in predominant mitral insufficiency, in mitral stenosis with concomitant aortic valve damage, and in arterial hypertension. Thus, we consider an increased VRB in a case of mitral stenosis with a low VQ to be suggestive of a complicating lesion of the left ventricle. The size of the left ventricular wall can also serve as a diagnostic aid. The thicker wall of the left ventricle in mitral insufficiency and in mitral stenosis complicated by aortic disease, as compared with that in uncomplicated mitral stenosis, is a radiologic demonstration of the hypertrophy.

In the present material, angiocardiography was performed to some extent in diagnostically well-defined cases. In all cases except two there was very good agreement between the clinical and angiocardiographic findings. Ten patients were operated on, and in these cases the angiocardiographic diagnosis was verified. In one case autopsy verified the angiocardiographic findings.

Angiocardiography involves certain risks, and should be used only in those cases of suspected mitral disease in which it might give information of value for the diagnosis or treatment. In pure cases of mitral stenosis with typical physical findings and a normal sized or slightly enlarged heart, angiocardiography is probably not necessary for the clinical evaluation. But in less well-defined cases with atypical clinical findings, or when the conventional films of the chest have shown a considerably enlarged ventricular portion of the heart, there is an indication for performing angiocardiography. By means of this examination an unsuspected mitral insufficiency may be revealed and a dangerous commissurotomy thereby avoided.

SUMMARY

The authors review the history of angiocardiography in mitral disease. They describe their own investigations and technique in the demonstration of the left side of the heart in which they employed injection into the pulmonary artery. The angiocardiographic findings in the various parts of the lesser circulation and in the left heart are discussed and illustrated. The differential diagnosis between mitral stenosis and insufficiency with special reference to the appropriate methods is considered.

ZUSAMMENFASSUNG

Die Verfasser geben eine historische Übersicht über die Angiographie bei Mitralserkrankungen. Sie beschreiben eigene Untersuchungen und ihre Technik für die Darstellung der linken Herzseite, in welcher sie Injektionen in die Arteria pulmonalis zu machen pflegten. Die angiographische Befunde in den verschiedenen Abschnitten des kleinen Kreislaufes und in der linken Herzhälfte werden besprochen und illustriert. Die Differentialdiagnose zwischen Mitralisstenose und Mitralisinsuffiziens wird unter besonderer Berücksichtigung der zweckmässigen Methoden kritisch betrachtet.

RÉSUMÉ

Les auteurs rappellent l'historique de l'angiocardiographie dans la maladie mitrale. Ils décrivent leurs propres recherches et leur technique pour mettre en évidence le coeur gauche, pour lequel ils ont utilisé l'injection dans l'artère pulmonaire. Ils étudient les aspects angiocardiographiques des diverses parties de la petite circulation et du coeur gauche et en donnent des exemples. Ils examinent le diagnostic différentiel entre sténose mitrale et insuffisance, et particulièrement les méthodes appropriées.

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THE STRAIN OBSTRUCTION SYNDROME OF THE FEMORAL VEIN

by

Åke Gullmo

In an earlier paper (1956) on the technique of phlebography of the leg the author stressed the importance of examining the veins in the inguinal region in a special way, namely during straining in the supine position. The principle of the method is briefly as follows. The patient is instructed to strain, during which 20 ml of contrast medium is injected. Straining in association with the injection pressure forces the medium into any dilated and incompetent veins of the leg, which in the supine position are otherwise fairly empty.

It was soon observed, however, that in patients with venous disorders of the leg straining was often accompanied by complete obstruction of the femoral vein in the lacuna vasorum. The compression was usually typical in appearance (Figs. 4, 5, 10, 11, 12, 13). In other cases the vein was impressed on the medial side or displaced laterally. In the absence of straining the femoral vein always has a practically straight course, even in those cases where the vein is totally compressed on straining (Figs. 4, 12, 13).

Anatomy of the lacuna vasorum

Previous investigations. McVay and Anson (1949), Zieman (1950) and Burton (1949—1956) examined the anatomic structures involved in inguinal and femoral hernias and stressed the importance of using the strong superior pubic ligament (Cooper's lig., described 1804) in their repair. This was suggested by Lotheissen as far back as 1898 and by Babcock (1927). The new concepts are based on the facts that in both inguinal and femoral hernias there is a weakness in the 'posterior wall'

Submitted for publication 9 July 1956.

of the inguinal canal which is formed mainly by the transversalis fascia. In femoral hernias there is also a weakness of the conjoined tendon, which consists of parts of the transversalis and the internal oblique aponeurosis (IASON 1941); furthermore the medial ligamentous wall of the lacuna vasorum (also called Gimbernat's ligament) becomes distended and attenuated at the expense of the breadth of the conjoined tendon and its normal anchorage on the ligament of Cooper is displaced medially. Recurrent hernia was often found in that part of the lacuna vasorum medial to the femoral vein (BURTON 1954, 1956). BURTON (1954) called this point the 'vulnerable space' or 'transitional angle' (Fig. 3), which also includes the septum anuli femoralis, which is part of the transversalis fascia and forms a packing layer in the medial part of the lacuna vasorum (also called the *lacuna lymphatica*); as a funnel-shaped continuation it also surrounds the femoral vessels as the femoral sheath, the vagina femoralis (COOPER 1837, NARATH 1899, IASON 1941), down through the lacuna vasorum (Fig. 3 b). The great lymphatic vessels of the leg pass through these fascial structures medial to the femoral vein. In femoral hernia the lacuna lymphatica is replaced by the 'femoral canal' although normally no canal exists (COOPER 1837, NICAISE 1889). Obviously there is a very close relation between the structures involved in hernias (direct inguinal and crural) and of the femoral vein and the lymphatics of the leg.

Author's investigation. At 25 autopsies the inguinal regions were explored and palpated from within. In normal cases the great vessels ran almost directly in the sagittal plane from the aorta and the caval vein down behind the inguinal ligament to the thigh. In elderly and emaciated subjects there was a slight angulation over the pecten ossis pubis.

Two cases were found to be of special interest in this connection. In a 73-year-old woman in whom a medial hernia was found, the sac was as large as a thumb hanging down medially over Poupart's ligament. There was also weakness in the lacuna lymphatica. With the finger in this 'vulnerable space' it was possible to compress the vein and obtain total obstruction when blood was forced upwards against the compression. Furthermore, the long saphenous vein was markedly dilated and contained a solid striated thrombus up to the confluence in the fossa ovalis. The femoral vein was normal.

Another woman, aged 55, had some years previously been operated upon for femoral hernia. As far as the femoral vein and the inguinal wall were concerned the hernioplasty was satisfactory, although in a very small area the bladder was adherent to the peritoneal scar. There was no sign of venous disorder on that side. The other side showed massive saphenous varicosities and a minor femoral hernia (not previously operated upon). Typical compression could here be demonstrated.

In about half the cases the internal oblique muscle had a muscular 'arcuate division' down in the inguinal region (KRIEG 1953). In the other half it was aponeurotic only. The hernial outlets seemed to be sealed better in the cases with more muscular teguments. In the aponeurotic cases it was often possible to insert the finger tip well down through the medial part of the lacuna vasorum. Even in the absence of demonstrable herniation the possibility of subperitoneal structures (the bladder, lymphatic glands and fat), acting on the vein by bulging down in the vulnerable space must be considered.

Phlebography

The material consisted of 302 patients (370 legs) examined for venous disorders in one leg or in both and 30 patients without known venous lesions. In the latter group phlebography was performed in combination with the injection of contrast medium for excretion urography. Fifty-two (52) legs with venous abnormalities were not accepted for the present investigation because the portion of the femoral vein in the lacuna vasorum could not, for technical reasons, be properly evaluated.

Patients without varicose disorders of the leg. It was soon observed that in a fair number of patients referred for urography the inguinal teguments or leg veins were pathologically changed. Thirty (30) controls could, however, be collected. In 18, straining produced no change in the appearance of the femoral vein in the lacuna vasorum (Fig. 1). In 2, it produced 'valvular occlusion' (see below, Fig. 7). In 8, there was a slight lateral displacement of the vein on straining. Most of these 8 patients, however, were either obese or fairly lean. The most obvious displacement was seen in the case depicted in Fig. 2. None of the controls showed signs of impression or compression. In 1 case only (Fig. 3), a slight retrograde flow in the long saphenous vein was seen on straining.

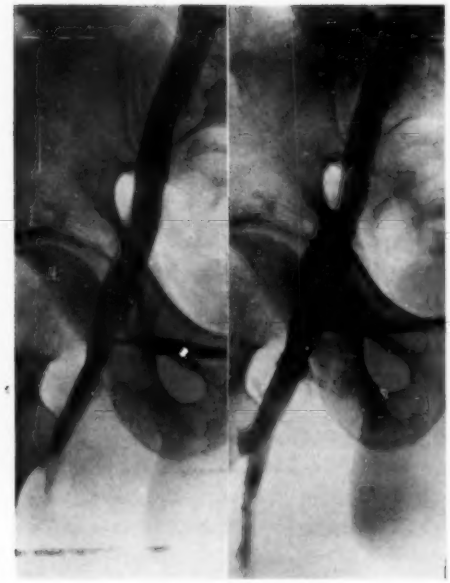
Patients with venous disorders of the leg. In Table I these cases are grouped according to the changes, if any, of the femoral vein in the lacuna vasorum on straining.

Out of the 370 legs examined (302 patients) straining produced total compression (Figs. 4, 5, 10, 11, 12, 13) in 100 (87 patients). In such totally obstructed cases the contrast density is always optimal right up to the obstruction, because there is no admixture of blood from above or below as long as the straining produces total obstruction. As will later be apparent, this group represented cases with the most advanced venous disorders.

Table I

The number of legs grouped as to changes in the femoral vein in the lacuna vasorum on straining

Obstruction tendency	Primary varicosities		Postthrombotic legs		Total	
Total compression	84		16		100	
Impression and displacement	66		10		76	
Impression	17		5		22	
Valvular occlusion	18	185	7	38	25	223
Displacement only	58		3		61	
Retrograde flow only	28		10		38	
Normal course of vein	31	117	17	30	48	147
Total number of legs		302		68		370



a b

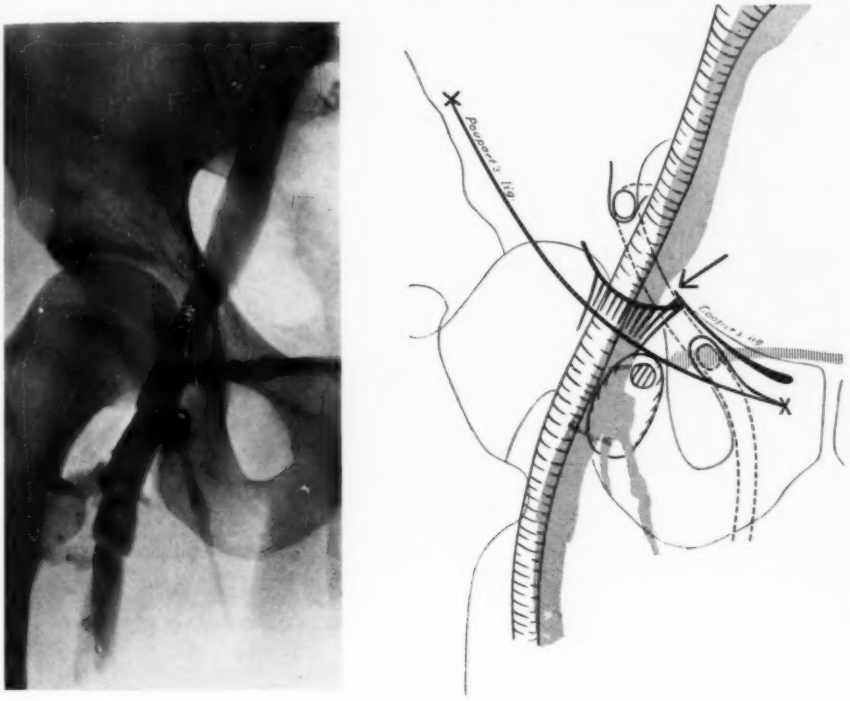
Fig. 1. Man, aged 42. Normal case. a) Without, and b) with straining. No changes of the vein in the lacuna vasorum.

a b

Fig. 2. Man, aged 28. a) Without, and b) with straining. The most advanced lateral displacement in the normal cases. Valve in the iliac vein.

The frequency of complete compression is given below. The next two groups included cases with partial compression (Fig. 6 b), but in many of these cases the compression on exertion, such as the lifting of a heavy weight, could become complete. In some cases an impression was demonstrable in the frontal plane by a hernia bulging just behind or, occasionally, in the front of the vein. It was seen as a decrease in the contrast density at the level of the lacuna vasorum. In such cases a lateral view may better demonstrate the degree of compression.

	Patients	Bilateral compression	Examined bilaterally	Legs	Right side	Left side
Women	50	8	15	58	34	24
Men	37	5	12	42	15	27
	87	13		100	49	51

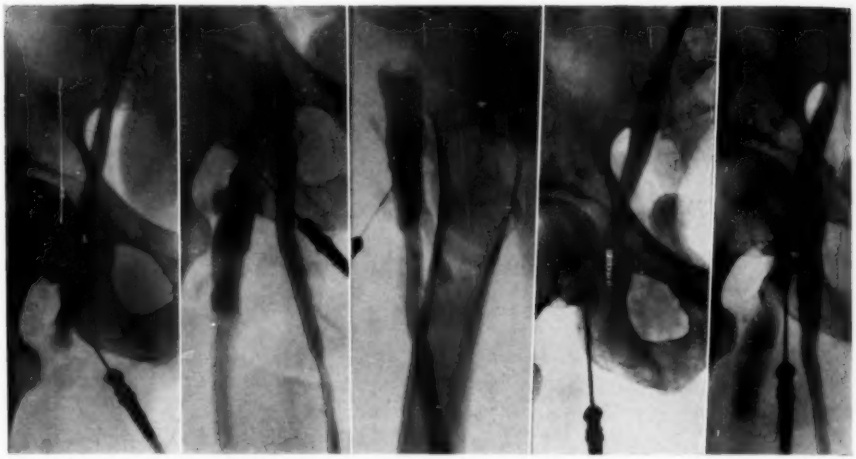


a b

Fig. 3. Man, aged 25. Normal case. Some filling also in upper part of long saphenous vein. b) Sketch of anatomic structures of importance. Vulnerable space (lacuna lymphatica) indicated by arrow. Lymphatic gland shown medially to femoral vein in fossa ovalis. Spermatic cord stippled.

One group is called valvular occlusion. This phenomenon can be better understood if the caval veins are considered as a venous cistern (KEITH 1908) with its lowest point at the sub-Poupartian valve. On straining the pressure increase in this cistern may in some subjects be so large that, in contrast to what is seen in normal legs (Fig. 1), the occlusion of the valve is not overcome by the injection pressure from below. According to the principle of the method used by the author the needle as a rule is inserted below the valve. If inserted higher up it would interfere with the behaviour of the vein in the lacuna vasorum.

The valvular occlusion phenomenon may represent an initial stage of venous disorders of the leg. In such cases every effort (including coughing and movement of the trunk) distends the venous column which then acts as a water-hammer in the femoral ring (KEITH 1923—24). This may in time give way to a hernial protrusion of the femoral type with compression of the vein proximal to the valvular occlusion. In these more advanced cases a small quantity of blood may be entrapped between the region of compression and the occluded valve. The compression is indicated by the lateral displacement of the vein at the site of the occluded valve on straining (Fig. 8 b) and occasionally



a b c d e

Fig. 4. Woman, aged 45. Strain compression. a) Without, and b) with straining. c) Lateral view with straining. Compression of the vein from behind. d) and e) One month after hernioplasty, McVay method (vesical hernia behind vein). Now normal course of the vein even on straining (e). Incompetent long saphenous vein not resected.

by a slight admixture of contrast medium proximal to the valve in the entrapped part of the vein (Fig. 9).

In the controls with valvular occlusion (Fig. 7), there was a proximal passage through the obturatorius collateral venous circle (BRAUNE 1873). In pathologic cases, however, this collateral circle was often filled only in its segment outside the obturatorius membrane (Fig. 8). On straining the vein seemed to be compressed in the course of its passage through the obturator canal. This might have been caused by laxity of the pelvic fascia, which is a continuation of the transversalis fascia of the posterior inguinal wall (ZIEMAN 1950).

The valvular occlusion group contained cases of mild or moderate varicose disorders, mostly long saphenous incompetence.

These first 4 groups are called the obstruction tendency cases as the total compression is in reality intermittent.

The displacement group without narrowing of the lumen of the femoral vein contained cases of only the milder forms of varicose disorders. The group 'retrograde flow only' certainly contained many cases with a varying degree of compression of the vein in the lacuna vasorum. This compression, if any, was at the moment not complete, since there was actually a downward flow. These cases were therefore included in this series, even though no filling was obtained of the vein in the lacuna vasorum. Most of them were seen in the beginning of the present investigation when interest was not focussed especially on the lacuna vasorum,

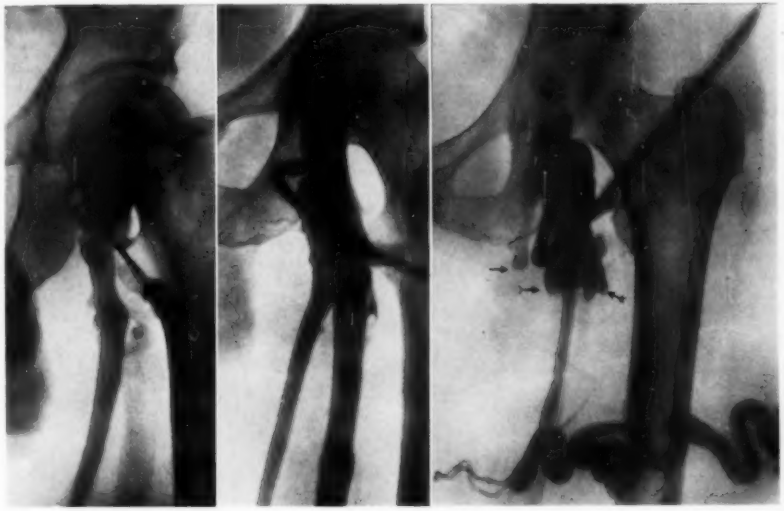


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Fig. 5. Strain compression cases. a) Man, aged 69, and b) Man, aged 40. Long saphenous incompetence and also incompetence of femoral vein. c) Woman, aged 44. Incompetence of an accessory saphenous vein. At →, competent valve in 'ordinary' long saphenous vein. At ⟩⟶, valve in femoral vein and ⟩⟶ valves in deep femoral vein.

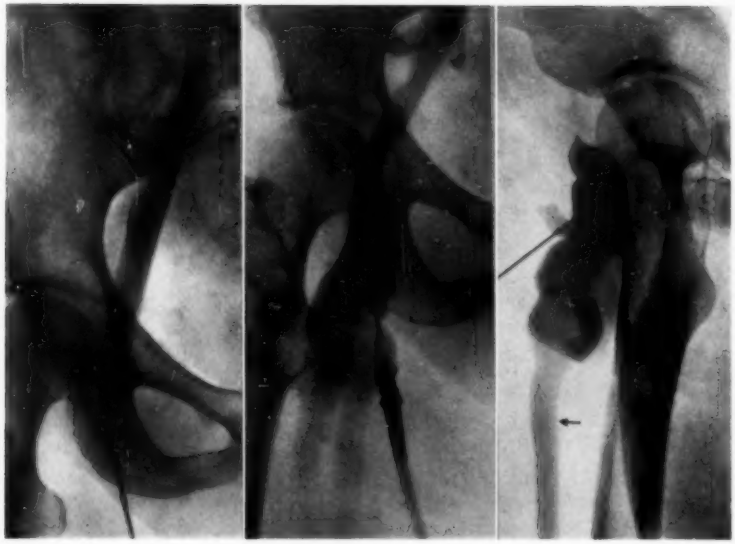
and the examinations were not repeated by a modified technique according to which the injection of the contrast medium was started some seconds before the patient began to strain.

Normal behaviour of the femoral vein in the lacuna vasorum was noted in only 48 out of 370 legs with venous disorders. Of these 48 legs 17 showed postthrombotic changes in the femoral vein.

The literature on phlebography contained no reports of changes in the femoral vein caused by hernias. WATSON (1948) mentioned that large femoral hernias may cause varicosities in the long saphenous vein by direct pressure upon it in the femoral region. KAPLAN (1941) suggested that "the pressure of Poupart's ligament on the femoral vein when the patient is in the prone position" could arrest the flow in the vein.

A few patients in this series were examined also in the prone position. No signs of compression caused by Poupart's ligament were seen. Fifteen (15) cases were examined in the erect position too. As to the compression phenomenon the findings were the same as in the supine position.

Sequelae of the strain obstruction syndrome. A primary weakness of the mesenchyma is commonly referred to as a cause of primary vari-



a b c

Fig. 6. Woman, aged 39. a) Without, and b) with straining: Moderate impression in the vein. c) Lateral view. Same side. Complete obstruction of vein by more effective straining. Attachement of sub-Poupartian valve is seen 1 cm below the compression. Incompetence of long saphenous vein (→).

cosities. The laxity of the inguina is also a manifestation of mesenchymal weakness. If the last state results in strain obstruction of the femoral vein, this may in turn initiate a vicious circle of venous disorders of the leg. The mechanism is a combination of a manifested strain-obstruction and a powerful squeezing out of blood from the calf muscles on exertion. On contraction of the soleus muscle, its great venous arches are vigorously emptied up through the popliteal vein (easily observed during fluoroscopy and which we have recorded by cineroentgenography). The soleus muscle veins give the impression of being the 'venous heart' of the leg. Many everyday physical exertions involve a Valsalva manoeuvre and in addition produce contraction of the calf muscles. The strain obstruction thus favours a sudden powerful pressure rise in the deep veins of the leg including the soleus muscle veins proper. This leads to the formation of pathologic pressure outlets by distention of the saphenous veins, as well as the communicating veins. Should these 'Windkessel' possibilities be inefficacious or previously removed by operation, the deep veins of the leg may become acutely distended, resulting in intimal lesions or

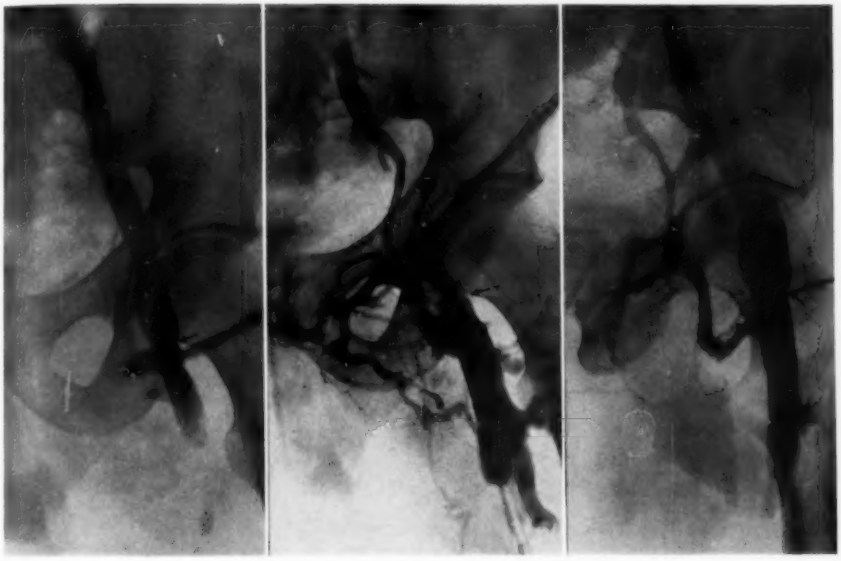


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Fig. 7. Man, aged 28. Normal case. Valvular occlusion. At → valve proximal to the needle in the femoral vein. a) Without, and b) with hard straining: Valve occluded. c) Oblique lateral view. Moderate straining. Incomplete valvular occlusion. In b) and c) medium filling of obturatorius collateral venous circle.

even rupture of a vessel, bleeding, and the initiation of acute thrombosis. As will be shown, there is also a strong tendency for varicosities to recur in obstruction cases, probably as an indication of the need of pressure outlets. These different and often combined manifestations of venous disorders in this condition, which I should like to call the 'strain obstruction syndrome', are discussed in the following.

Incompetence of the long saphenous vein. Out of the 100 legs with total compression there were: 45 with incompetence of the long saphenous vein (Figs. 5 a, b); 10 with incompetence of an accessory saphenous vein (Fig. 5 c); 34 which were previously operated upon (high saphenous resection); 11 with saphenous valves still competent (Fig. 10).

Out of the 34 legs previously submitted to operation (which in many cases included stripping) there were 26 with recurrences. Of these, 15 were of the type shown in Fig. 12; these I should like to call 'compression recurrences' as they were only found in cases with total compression. The other 11 recurrences were of the overbridging type (Fig. 11) with

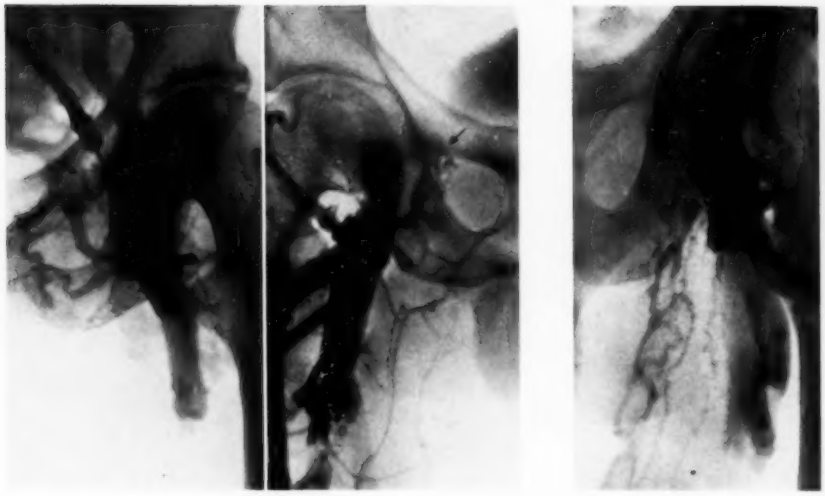

Fig. 8 a b Fig. 9

Fig. 8. a) Woman, aged 64. Strain compression (incomplete). b) Man aged 40 (same case as Fig. 10). Right side. Valvular occlusion. In both cases compression of obturatorius collateral venous circle at → (inner margin of obturatorius canal). In b) the sub-Poupartian valve seems to be tricuspidal.

Fig. 9. Man, aged 50. Valvular occlusion. Incompetent long saphenous vein had been resected and stripped two months previously. Bundles of valveless veins in its course indicates tendency to obstruction recurrence.

the resected part of the vein renewed by a single tortuous vessel of about the same calibre as the original vessel. Only in 8 legs were no recurrences seen. In all of these non-recurrent cases, however, some other form of pressure outlet had formed, such as incompetence of the short saphenous vein. In all there were 81 legs (45 + 10 + 26) out of 100 with some form of phlebographically demonstrable pressure outlet by incompetent superficial veins in the groin.

Incompetence of the short saphenous vein. This pressure outlet possibility was found in 33 cases out of the 100 legs with total compression. Of these, 17 had also long saphenous incompetence. Varicose degeneration of the short saphenous vein was often most pronounced in the popliteal fossa, it being nearest to the pressure waves in the popliteal vein. In the other groups in the series, short saphenous incompetence was uncommon and seen mostly as only a moderate dilatation of this vein.

Varicosities in the soleus muscle veins. The author has seen varicosities in no muscle veins other than those in the calves (the soleus and gas-

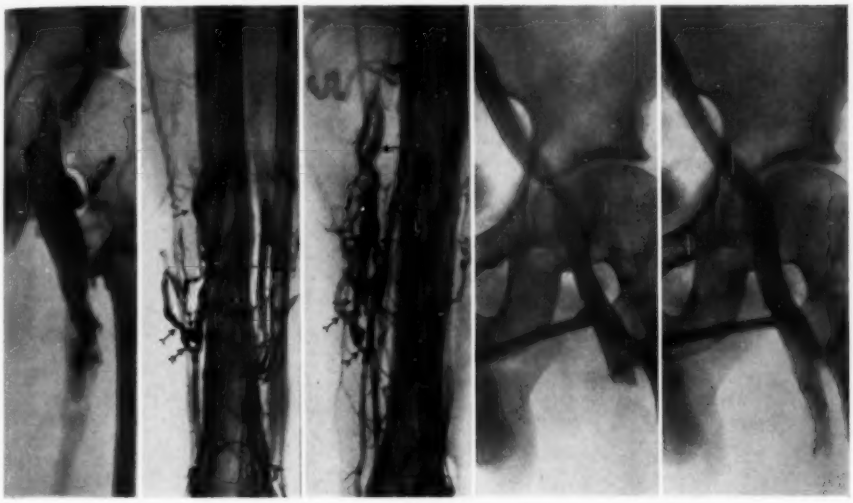

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Fig. 10. Man, aged 40. Strain compression with acute bleeding of calf muscle. a) With straining: Total compression and some incompetency of valves in femoral vein. Competent valves in long saphenous. b) and c) Lower leg. At →, dilated and avalvular soleus vein. At →→, incompetent communicating vein from lower part of this soleus vein. At »→, inferior communication with posterior tibial vein. In c) also filling of small plexiform and irregular soleus veins. Maximal local tenderness over this area and supposed original site of bleeding. d) and e) After hernioplasty no compression (McVay method. Small femoral hernia with 'lipome herniaire'). Moderate lateral displacement on straining (e) and also without straining (d) seems to be postoperative effect. Valves in the femoral vein have become competent.

trocnemius muscle veins). Fluoroscopy has shown that in the beginning the dilatation of the veins in the soleus muscle may be compensatory, since these veins empty completely on contraction; on relaxation, however, they immediately refill from above.

Of the 223 legs with obstruction tendency the soleus muscle veins were of postthrombotic appearance (valveless, irregular and plexiform) in 70; valveless and varicose in 51; obviously dilated with reduced number of valves in 73; practically of normal appearance in 12; not examined or no filling obtained in 17.

It should be noted that in Table I only cases with postthrombotic changes in the long deep veins were placed in the 'postthrombotic' group. Thirty-nine (39) legs with signs of postthrombotic changes only in the soleus muscle veins were therefore placed into the primary varicosities group.

The great number of soleus muscle vein changes in the obstruction

Fig. 11. Woman, aged 53. Strain compression. Overbridging tortuous recurrence of long saphenous following high resection, rather low down.

cases argues for their participation in the syndrome. Of the total compression cases many legs were found with a greatly increased number of varicose venous arches in the belly of the soleus muscle almost giving it the appearance of a venous sponge. This accumulation of large venous sinuses in the soleus muscle is of somewhat the same nature as the compression recurrences in the groin.

In the displacement group there were, on the other hand, 23 legs out of 61 with practically normal soleus muscular veins, in 22 they were slightly dilated, and in 6 and 5 they were varicose or postthrombotic, respectively. In 5 the lower leg was not examined.

Varicosities of the gastrocnemius muscle veins seem more often to be secondary to superficial varicosities in long saphenous incompetence. The perforating veins over the lower medial pole of this muscle are at first seen to be dilated, the incompetence in more advanced cases then extending proximally in the gastrocnemius muscle veins proper.

Incompetence of the communicating veins of the lower leg. In 145 out of the 223 legs with an obstruction tendency there was a dilated and valveless communicating vein at the level of the lower point of the venous arches in the soleus muscle (Figs. 11 b, c). This is situated about 10 to 15 cm proximal to the medial malleolus (GULLMO 1955, 1956) and is called 'the upper internal ankle perforating vein' by DODD and COCKETT (1956). The strain obstruction seems to be the cause of 'blow-outs' at this point. In all of these 145 legs some changes were also seen in the soleus muscle veins.

Incompetent communicant veins in the low malleolar region ('the lowest perforator') was only found in 31 legs out of 370 in this series. They were most common in the post-thrombotic cases (16 legs) in the non-obstruction groups. This low 'ankle blow-out syndrome' (COCKETT and JONES 1953) usually seems to be a pressure outlet manifestation in postthrombotic cases and is not related to the obstruction syndrome.

Acute bleedings of the leg. A case will now be described to illustrate the possibility of the obstruction syndrome being a causative factor in bleeding in the calf by rupture of soleus muscle veins (Fig. 10).

a b c d e

Fig. 12. Woman, aged 57. a) Without, and b) with straining. Extensive compression recurrence. High resection performed twice before. c) Left side: High resection for the third time two months previously; already typical recurrence. d) Woman, aged 51. More advanced strain compression recurrence. e) Woman, aged 52. Same findings. Patient had had a large subcutaneous bleeding in thigh.

A male, aged 46, of strong muscular habitus had for some years had somewhat dilated veins in both legs. In January 1956 he lifted a heavy weight (*i. e.* a Valsalva manoeuvre combined with soleus muscle contraction) following which he experienced a strange sensation of 'flooding' in the left calf and was soon (not suddenly) unable to walk because of cramp. The calf became somewhat swollen and after 3 days a haemorrhagic discolouration of the skin was seen both medial and lateral to the belly of the soleus muscle; the Achilles tendon could be stretched passively in a normal way. Phlebography on the third day after the bleeding showed a typical strain compression (Fig. 10 a) but no signs of thrombosis of the deep veins in the lower leg (Figs. 10 b, c). The soleus muscle veins, however, showed changes which, in my opinion, were secondary to overdistension by strain obstruction. The patient received vigorous anti-coagulant therapy. Operation one month later revealed a dilated femoral ring and a lipomatous mass medial to the vein. On phlebographic control one month later (Figs. 10 d, e) there was no longer any compression. A slight lateral displacement of the vein seemed to be caused by the hernioplasty, since it was also seen without straining.

In many cases with earlier spontaneous thrombosis the patient described haemorrhagic discolouration of the calf at the onset of the thrombosis.

The first inspection in 2 of the 15 cases of compression recurrence

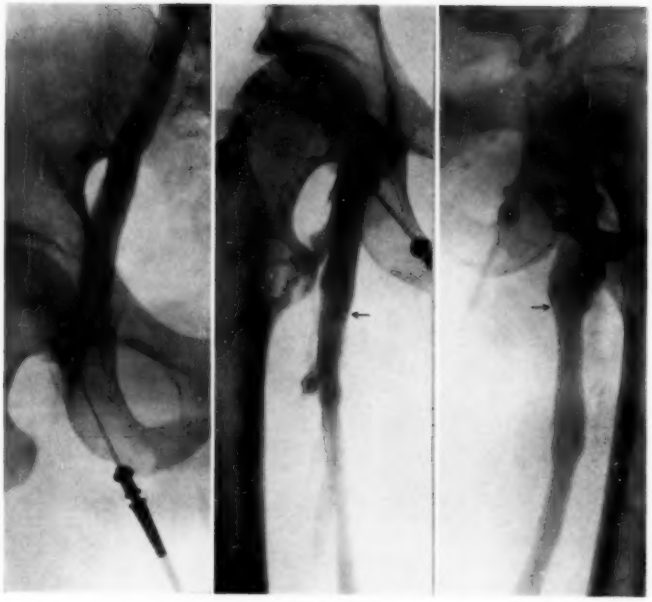

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Fig. 13. Man, aged 36. a) Without, and b) with straining. c) Woman, aged 65. With straining. In both cases strain compression and postthrombotic changes up to the upper third of femoral vein. At → valves, however, incompetent. In c) some filling also of long saphenous and superficial inferior epigastric veins.

showed large subcutaneous bleedings (ecchymoses) in the lower anterior part of the thigh (Fig. 12 e). The cause of bleeding could here have been a rupture of a superficial pressure outlet vein.

Lesions in the soleus muscle veins seem to be the most common origin of thrombosis. This is also in accordance with the autopsy findings of RÖSSLE (1937) and NEUMANN (1938). In cases with postthrombotic changes in the femoral vein the obstruction cases differed in appearance from those in the non-obstruction cases. In the former they usually extended only up to the upper third of the femoral vein (Fig. 13), the veins in the inguinal region and pelvis being normal in this respect. In the non-obstruction cases these changes usually extended up through the lacuna vasorum. This difference in the picture suggests another cause of the thrombosis in the cases without signs of obstruction. The high incidence of thrombosis in the obstruction groups, as compared to the displacement group, may also suggest a direct relation between the obstruction syndrome and thrombosis.

In at least 5 total compression legs there had been spontaneous deep thrombosis of the leg within a few months (not immediately) after a previous high saphenous resection.

Brawny induration and ulcerations of the lower leg. Many patients with postthrombotic recanalization of the deep veins and without signs of strain obstruction had a normal skin of the leg except a tendency to depilation and, at times, minor ulceration in the malleolar region. On the other hand the most advanced venous disorders with brawny indurations and large ulcerations were found among the total compression cases and sometimes among the obstruction tendency cases. The strain obstruction mechanism seems to be the main cause of these advanced leg disorders. Many such cases were found to have rather normal deep veins with the postthrombotic changes, if any, situated only in the soleus muscle veins.

The cause of the brawny indurations seems to be repeated minor bleedings from ruptures of calf muscle veins or perhaps more often from ruptures of small veins in the superficial area of a pressure outlet communicating vein.

Observations upon therapy

Fifteen legs in this series have as yet been operated upon with 'ligament of Cooper hernioplasty' and repair of the lacuna vasorum (Figs. 4 and 10). In some cases there was no real hernia but merely a weakness in the 'posterior inguinal wall' which was bulging down against the proximal inlet of the lacuna vasorum. The results are in all cases very encouraging. The older methods, of BASSINI, HALSTED and GIRARD, for example, should not be used. In these, only the inguinal ligament is used for the fascial duplication and reinforcement. This ligament has a movable lower margin and allows a bulging downwards on straining. In some cases operated upon by the Girard method the strain obstruction changes were unaltered on postoperative phlebographic control. In the new hernioplasty methods devised by MCVAY and ANSON (1942, 1949) and elaborated further by BURTON (1954—1956) the primary fault, the laxity of the transversalis fascia in the posterior inguinal wall, is repaired and the available abdominal wall joined to the firm superior pubic ligament of Cooper. These methods were intended to prevent recurrence of herniation. They may prove of more importance in the causal therapy of venous disorders of the leg. Certain modifications of the methods may perhaps be necessary for the accomplishment of a free and secure passage of the vein through the lacuna vasorum.

In some cases the compression seemed to be caused by a 'lipome herniaire' (VERDIER 1752, CAUBET 1903, JABOULAY and PATEL 1908,

KEITH 1923—24, WATSON 1948). On removing such a lipoma from the 'vulnerable space' the lymphatics of the leg should if possible be spared.

In order to prevent irreversible damage to the leg veins the possibility of strain obstruction requires early elimination. Spontaneous bleedings and 'bursting pains' in the calf as the day wears on should be signals for proper examination.

Deep vein ligation, including popliteal vein resection (PARONA 1904, LERICHE 1923, HOMANS 1941, BAUER 1947, 1948, LINTON and HARDY 1948), in these very common cases only brings the obstruction to a lower level and makes it permanent. BOYD and coll. (1953) proved these methods to be ineffective and even harmful.

SUMMARY

The author describes the strain obstruction syndrome consisting of a blocking of the femoral vein in the lacuna vasorum during strain by hernial protrusions. Out of 370 legs with venous disorders, 223 (60 %) showed a tendency to strain obstruction, and of these 100 (27 %) had complete compression of the vein. The syndrome was demonstrated in the cases with the most advanced venous disorders in the series. It is shown to be the usual cause of recurrence after high saphenous resections. It may cause spontaneous bleedings in the leg and seems to be the cause of thrombosis in normal active persons. The treatment is discussed.

ZUSAMMENFASSUNG

Der Verfasser beschreibt das durch Muskelspannung erzeugte Obstruktionssyndrom, welches in einer Blockade der Femoralvenen in der Lacuna vasorum durch herniale Protrusion während der Spannung besteht. Von 370 Beinen mit venösen Erkrankungen zeigten 223 (60 %) eine Tendenz zur Spannungsobstruktion und von diesen hatten 100 (27 %) eine vollständige Kompression der Vene. Das Syndrom wurde in den Fällen mit den fortgeschrittensten Venenerkrankungen der Serie gefunden. Es wird gezeigt, dass das Syndrom die gewöhnliche Ursache der Rezidive nach hohen Saphenaresektionen ist. Es kann spontane Blutungen in den Beinen hervorrufen und die Ursache der Thrombosen bei normalbeweglichen Personen sein. Die Behandlung wird besprochen.

RÉSUMÉ

L'auteur décrit le syndrome d'obstruction à l'effort consistant en un blocage de la veine fémorale au niveau de l'anneau crural pendant l'effort, par protrusion de hernie crurale. Sur 370 membres inférieurs atteints de troubles veineux, 223 (60 %) présentaient une tendance à l'obstruction d'effort, dont 100 (27 %) présentaient une compression complète de la veine. Ce syndrome a été mis en évidence sur les cas de cette série qui étaient atteints des troubles veineux les plus avancés. L'auteur montre que ce syndrome est la cause habituelle de récidive après les résections hautes de la saphène. Il peut causer des hématomes spontanés dans le membre inférieur et semble être la cause de thromboses chez des personnes ayant une activité normale. L'auteur discute le traitement.

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EXPERIMENTAL INVESTIGATIONS ON CATARACT FORMATION FOLLOWING WHOLE-BODY ROENTGEN IRRADIATION

by

Erik Poppe

Opacities of the lens after irradiation in man were mentioned as early as around the turn of the century (BIRCH-HIRSCHFELD 1904). Nevertheless, many years passed before it was definitely established that the lens is very radio-sensitive. As late as in 1938, DESJARDINS stated in a survey that roentgen doses which did not produce injuries to the conjunctiva or cornea would also not cause lasting changes in the lens. The cause of this erroneous opinion has most likely been the long period of latency from the moment of radiation up to the moment when the lens changes could be observed. In man, the latency period is from 2 to 5, even up to 12 years (MILNER 1934).

AULAMO (1928) and ROHSCHNEIDER (1929) were the first to produce cataract experimentally in animals after local roentgen irradiation of the eye.

The present writer in 1942, in an experimental study of rabbits, showed that local roentgen irradiation of the eye with doses as low as 250 r produced cataract. The opacities in the lens are manifested approximately 5 to 7 months after irradiation of the eye. The latency period is longer after smaller cataract-producing doses; the period of latency decreases after larger doses. The writer also described the *in vivo* and the histologic changes of the lens in rabbits after irradiation of the eye with doses of 100 r up to 3,000 r. The smallest cataract-producing dose (250 r) did not cause any gross changes in the remaining parts of the eye. It seems that

Submitted for publication 9 July 1956.

the lens is the most radio-sensitive part of the eye. The roentgen cataract is the result of a direct effect of the lens epithelium.

Since the Second World War, the appearance of cataract after ionizing radiation has been a subject of great interest (COGAN et DONALDSON 1951, VON SALLMANN et LOCKE 1951, HOWARD 1952).

Cataract has been described in subjects exposed to the atomic bombs in Japan (KIMURA & IKUI 1951, SHIGETO & MASUDA 1955). Likewise, cataract development has been reported in physicists and technicians exposed by accident to total-body irradiation with ionizing rays (HEMPELMANN et coll. 1952). Since the war no less than five 'Conferences on Radiation Cataract' have been held, at which problems connected with lens opacities after different forms of ionizing radiation have been described and discussed.

A series of observations indicate that the lens epithelium belongs to the most radio-sensitive tissues, and that cataract may occur after total-body irradiation with doses producing only very slight, or even no general signs (LEUCUTIA 1952).

The purpose of the present paper has been mainly to study the smallest cataract-producing doses after total-body irradiation, and investigate the possibility of causing cataract with doses which do not give rise to any other lasting damages detectable by ordinary clinical means.

The *in vivo* and pathologic-anatomic findings in the lens have therefore been registered and related to the epilation, the weight curve of the animals, and other general radiation signs. Furthermore, the fertility of the animals has been tested, and the germinal tissue histologically examined. A special effort has been made to examine the relative radiosensivity of the germinal epithelium and the lens epithelium. It should, however, be pointed out that only in certain stages in the development of the male germ cells are these very radio-sensitive, whereas the cells in other stages are rather radio-resistant. Likewise, in the testes a great number of the damaged cells are eliminated, whereas the lens fibre epithelium remains in the lens.

Adult male white rabbits were used for the experiments.

The material consists of 16 animals. The age at irradiation varied from 7 to 24 months. All the animals weighed more than 2 and most of them over 2.5 kg at the time of exposure. During the irradiation, the animals were placed in a box 14 by 15 by 25 cm with sides of thin wood. In the end wall was 'a breathing-hole' 2.5 cm in diameter. A roentgentherapy apparatus, type Müller R.T. 200, was used for the irradiation. Radiation factors have been the same for the whole series: 170 kV, 15 mA, filter 0.5 mm Cu, F.S.D. 70 cm, half-value layer 0.85 mm Cu. Two animals received fractioned irradiation and the remaining 14 were irradiated once. The doses were measured in air with a Moxnes dosimeter placed 10 cm above the bottom of the box, corresponding to the height of the rabbit's back. The same roentgen tube has been used for all experiments.

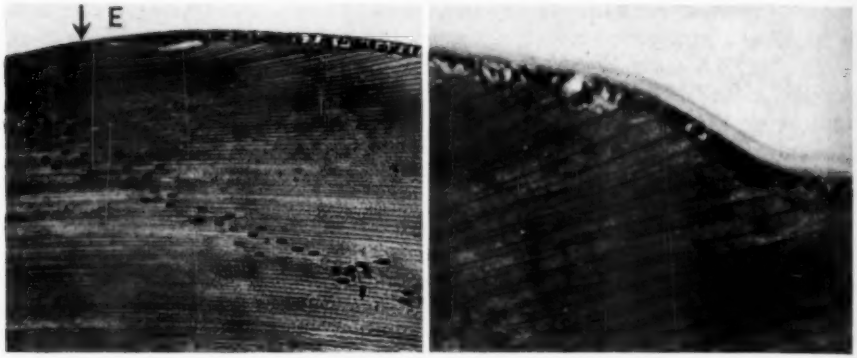


Fig. 1. Normal lens epithelium, showing the nuclear arch. Normal lens fibres. Magnification × 60, and × 200 (E, equatorial region).

All the animals were weighed and all the eyes examined in homatropine mydriasis before irradiation. This latter examination embraced the following methods: 1) external examination, 2) inspection by focused artificial light with a monocular loupe (Zeiss × 8), 3) transmitted light examination, 4) ophthalmoscopic examination of the eye ground ('Oculus' ophthalmoscope), 5) examination with slit lamp and cornea microscope (× 9).

In all the 16 rabbits, normal conditions were found during these examinations. Particular attention was paid that the media were clear. After irradiation, the animals were each week weighed and examined as to the general state of health and the hair growth. Examination of the eyes in homatropine mydriasis was made every 14th day after the roentgen treatment. The animals were killed by a blow on the head, or by decapitation after an observation period ranging from three-and-a-half to twenty-four months. Eleven animals lived more than 12 months, and 6 lived more than 20 months after the irradiation.

Pieces of the liver and pancreas were histologically examined in all animals. However, after the doses used, and with the relatively long period of observation following irradiation, the sections showed normal conditions.

The epithelium of the lens consists of a single cell layer covering the anterior surface of the lens (Fig. 1). The epithelial cells then curve back to the equatorial region (arrow E). Here the cells gradually become longer, and their nuclei form the so-called nuclear arch. This nuclear arch gradually decreases towards the center. When the lens fibres are fully developed they have no nuclei. Normally, nucleus-containing fibres are not found behind the equatorial region. The posterior surface of the lens behind the equatorial region is covered by the lens capsule only.

The histologic examination of the irradiated eyes was carried out through sections of the eye, with the lens *in situ*. The techniques employed were described in a previous paper (POPPE 1942).

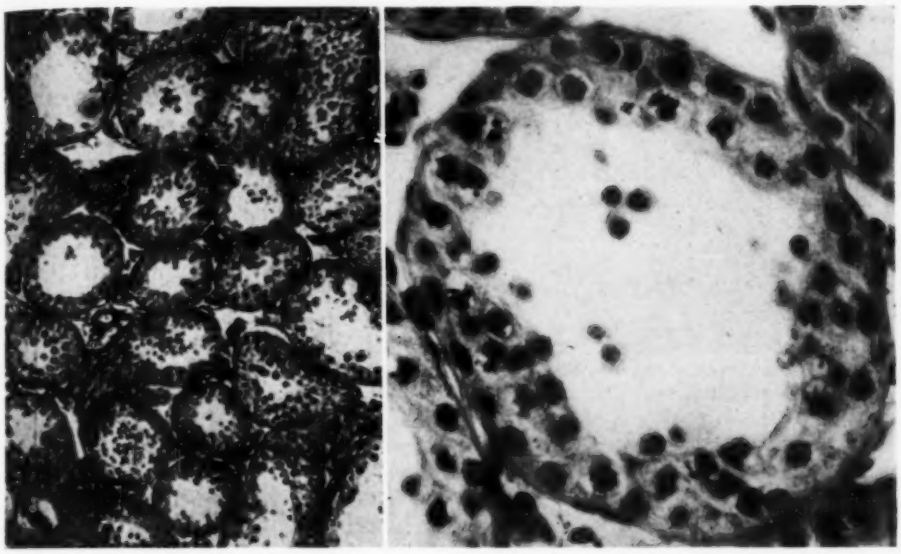


Fig. 2. Testes from Rabbit No. 9, 20 months after total-body irradiation with 200 r. Very few spermatozoa, irregular tubular lining, pycnotic and fragmented nuclei, and a great number of mitoses some irregular. × 30, and × 500.

Experimental results

Dose 200 r. Rabbits No. 9 and No. 10. Initial weight, both 2,800 g, this weight being maintained during the whole experiment. The general health was very good, the fur glossy. No epilation. Fertility was tested at 12, 17, and 24 (No. 10) months after irradiation. No offspring.

The testes showed tubuli with no, or very few, spermatozoa, slightly irregular tubular lining, pycnotic and fragmented nuclei, and a number of mitoses, some irregular (fig. 2).

In rabbit No. 9, fine subcortical opacities of the lens near the posterior pole (fig. 3) were observed six months after the irradiation. No other pathologic signs. The histologic changes at the termination of the experiment, 20 months later, consisted of slightly swollen lens fibres near the posterior pole (fig. 4). No other ocular changes.

In rabbit No. 10, with an observation period of 24 months, clear media and no histologic changes were found.

Dose 250 r. Rabbit No. 1, weight 2,270 g and rabbit No. 2, weight 2,450 g. The weights were maintained during the observation periods, which were 22 and 23 months, respectively. General health very good; fur normal.

Fertility tested 6 months after irradiation, and both animals produced litters. The offsprings were brother-to-sister mated for four generations with apparently normal animals. Testes were examined, and great numbers of spermatozoa, mainly normal in appearance, were found in both animals.

Ocular changes, consisting of fine sub-cortical opacities of the lens at the posterior pole, were observed 7 months after the irradiation in both animals (fig. 5). The opacities

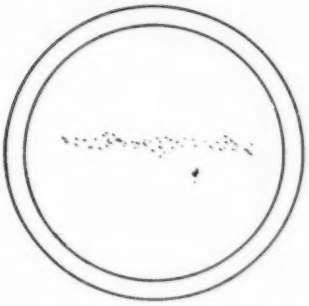


Fig. 3. *In vivo* observation of opacities in posterior cortex of the lens 6 months after the irradiation with 200 r in rabbit No. 9.

Fig. 5. *In vivo* observation of lens opacities in posterior cortex 7 months after the irradiation with 250 r in rabbit No. 1.

Fig. 4. Slightly swollen lens fibres in rabbit No. 9, at termination of experiment, 20 months after irradiation with 200 r. (P. C., posterior cortex near posterior pole.) × 200.

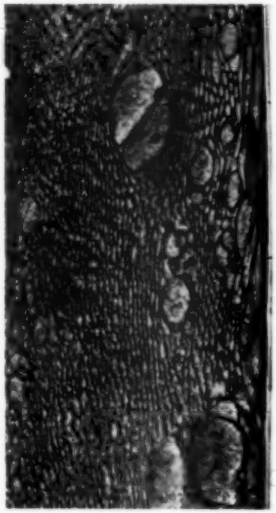
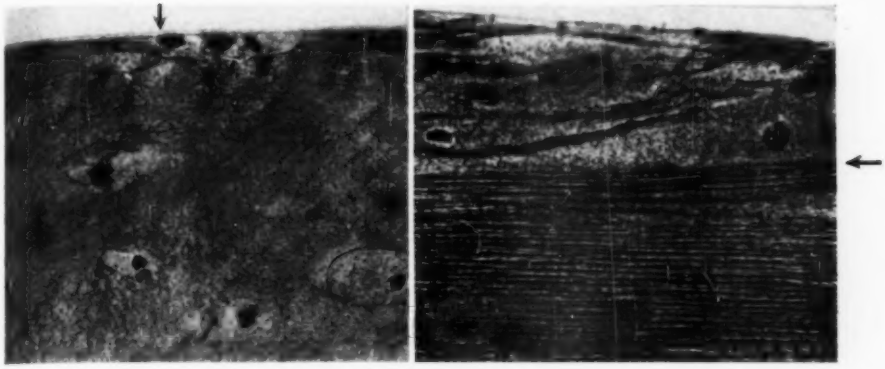


Fig. 6. Markedly swollen lens fibres in posterior cortex in rabbit No. 1, at termination of experiment, 22 months after the irradiation with 250 r. (P. P., posterior pole.) × 200.

did not progress during the 14 months of observation. Histologic examination revealed in all the four eyes swollen lens fibres, with nuclei behind the equator at the posterior pole (fig. 6). Other parts of the eyes were normal.



a b

Fig. 7. a) Markedly swollen nucleus containing lens fibres in posterior cortex (↓). b) In some areas a distinct limitation (←) toward layers of normal fibres. (From rabbit No. 8, at the termination of experiment, 17 months after a total-body irradiation with 400 r.) × 200.

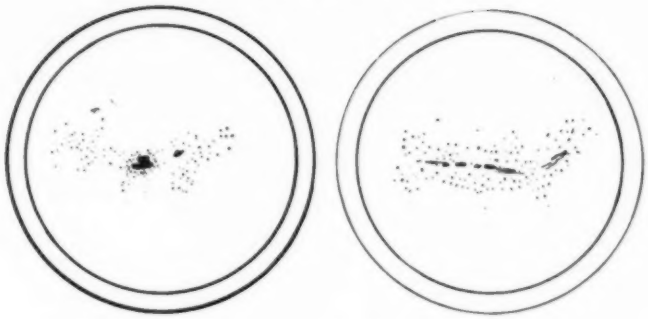
Dose 300 r. Rabbits No. 3 and No. 4, with initial weights of 2,650 g and 2,410 g, both living 21 months after the irradiation, and maintaining the initial weights. The fur and the general health were normal. The fertility was tested 7, 16, and 20 months after the irradiation, with no offspring. Histology of testes revealed few, or no spermatozoa in the different tubules. Some nuclei were hyperchromatic and some irregular mitoses were found.

After 9 months, opacities in the posterior pole were observed in both eyes of both animals but there were no other pathologic findings. The histologic examination showed, in all four eyes, the characteristic swollen lens fibres and the deformed nucleated fibres at the posterior pole.

Dose 400 r. Rabbits No. 5 and No. 8 weighed 3,210 g and 2,820 g, respectively, living 9 and 17 months after the irradiation. The general health was slightly influenced, with a moderate loss of weight and temporary partial epilation in the first. No. 8 showed normal appearances. The fertility was tested 5 and 14 (No. 8) months after the irradiation, with no offspring. Histologically, the testes showed minor changes. A great number of spermatozoa were present, but some of the other cells had swollen and clumped chromatin, and some irregular mitoses.

In No. 5, the characteristic opacities were observed after 6 months, in No. 8 after 14 months. No other ocular changes. The histologic examination (rabbit No. 8, fig. 7) revealed the same changes as described under dose 300 r.

Dose 500 r and 600 r. Rabbits No. 11 and No. 12 weighed 2,700 g and 2,500 g, respectively. Both lived 12 months after irradiation, maintaining more or less the initial weights. The fur was uneven, especially half a year after the irradiation, and some epilation was observed. The fertility was tested after 4 months, with no offspring. Testes were not examined. At 12 months, characteristic opacities were observed in both animals (fig. 8). The usual histologic changes were present. In the animal receiving 600 r, vacuoles, in addition, were seen in the anterior part of the area. No other ocular changes.



a b

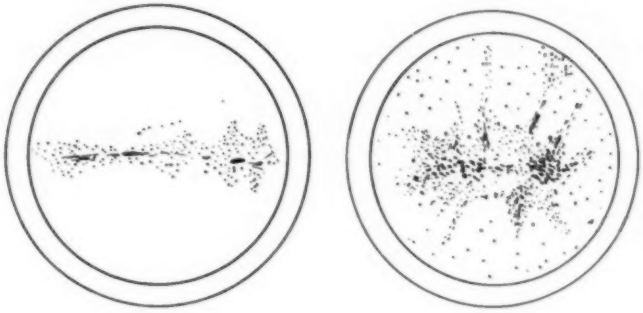
Fig. 8. *In vivo* observation of opacities 12 months after irradiation with 500 r in rabbit No. 11 (both eyes).

Dose 750 r. Rabbits No. 13 and No. 14 weighed 2,300 and 2,500 g, respectively, and both were alive 8 months after the irradiation. The general signs were slightly more pronounced as compared to the previous group, including a more marked epilation. No offspring when tested at 6 months. Testes not examined.

Opacities of the lens occurred in the two animals, 5 and 6 months, respectively, after the irradiation (fig. 9 a). After 8 months, the opacities involved the whole of the posterior cortical area (fig. 9 b).The histologic examination showed more marked changes as compared with the previous group. A considerable number of swollen nucleated fibres in the posterior cortical area, as well as an irregular nuclear arch, were found. No ocular changes outside the lens.

Dose 800 r. Rabbits No. 15 and No. 16, both weighing 2,500 g. The animals suffered a considerable loss in weight: 700 and 500 g, respectively, and the general health was poor, especially one month after the irradiation, with nearly total epilation of head and neck.

Rabbit No. 15 was killed after 3 months. At that time opacities were not seen, but swollen nucleated fibres were found histologically in the equatorial region posteriorly



a b

Fig. 9. *In vivo* observation of opacities in right eye of rabbit No. 14: a) 5 months and b) 8 months after total-body irradiation with 750 r.

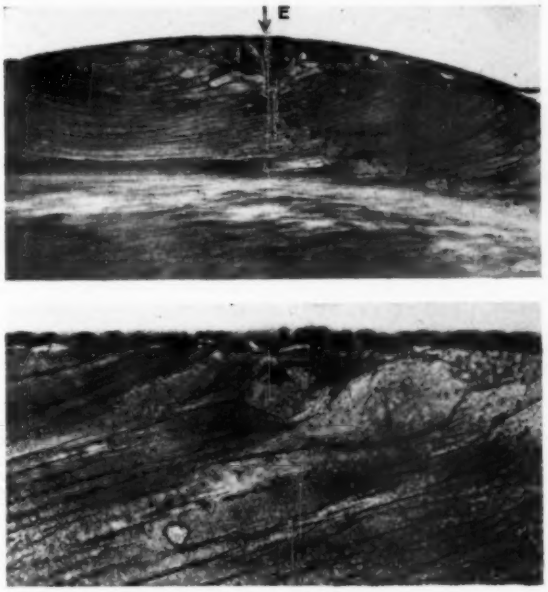


Fig. 10. *Top:* Swollen nucleated fibres in the equatorial region posteriorly (arrow E: aequator lentis; cf. fig. 1, left). × 60. *Below:* Detail of pathologic, swollen and nucleus containing lens fibres beneath the single layer of lens epithelium (cf. fig. 1, right). × 350.

(fig. 10). At the posterior pole, the lens fibres appeared normal, as could be expected from the short period of observation. In this animal, in addition, the cornea also showed pathologic changes with varying size of the nuclei. The remaining parts of the eye were normal.

Rabbit No. 16 died suddenly in a nearly marasmic state after three-and-a-half months, and the eyes showed autolytic changes to a degree preventing a histologic examination. Opacities had not been observed before the death of the animal.

Fractioned irradiation with 200 r in each of two series. Rabbits No. 6 and No. 7, both weighing 2,900 g. In one animal the doses were given with a 5-day interval, in the other, a 20-day interval. The animals were kept 12 and 18 months, and in both the fertility was tested at 11 months, and in one also after 17 months. No offspring. The general *in vivo* and histologic examinations in these animals revealed changes less marked than in those receiving 400 r in a single dose.

Discussion

The opacities in the lens after total-body irradiation have an appearance similar to the opacities occurring after local irradiation of the eye. After the lower doses, the period of latency in rabbits is approximately

half a year, that is, nearly one-eighth of the total lifetime of these animals. The opacities are seen especially in the posterior cortical area, just in front of the posterior pole. If the histologic examination is carried out in eyes, before opacities can be observed *in vivo*, the pathologic changes are localized particularly to the equatorial region, with an irregular nuclear arch, and with swollen nucleated fibres close and posterior to the equator. If the histologic examination is carried out after the occurrence of opacities, swollen nucleated fibres are found in the posterior cortical area.

Following total-body irradiation, opacities of the lens have been observed after doses as low as 200 r; these opacities have not shown progression in the periods of examination. With these lower doses, no other changes in the eye have been observed. The roentgen cataract is regarded as a direct radiation effect on the lens epithelium.

The equator lentis is the germinative zone of the lens epithelium. It is here the mitotic activity takes place (VON SALLMANN 1952, HOWARD 1952). The cells of the lens epithelium at the equator divide throughout a lifetime to give rise to new lens fibres. The fully developed lens fibres will in the normal way lose their nuclei gradually.

After radiation with cataract-producing doses, cells in the equatorial region are seen to be damaged. These cells form pathologic lens fibres which migrate or are pushed towards the posterior cortical pole. The pathologic lens fibres often contain nuclei. The anatomy of the lens does not permit the elimination of damaged or pathologic cells, but these will remain within the cortex or in the 'nucleus lentis' throughout life.

The germinative cells in the testis are constantly dividing, and have a very high mitotic activity. The various developmental stages manifest a very different radiosensitivity (REGAUD & LACASSAGNE 1927; MOHR 1919). In the testis, the fully differentiated cells are gradually eliminated. The testis, in contrast to the lens, will thus also be able to eliminate damaged and pathologic cells. The effect of the radiation of the testis with relatively small doses may therefore after a certain time be obscured.

The fertility of some of the rabbits in the present experiment has been maintained after a total-body irradiation of up to 250 r, in animals developing cataract. The lens epithelium, accordingly, may still reveal damage due to irradiation where the germinative epithelium has eliminated all the pathologic cells. After a certain time, the slight injury to the germinative cells is not detectable functionally through the absence of fertility, or morphologically by changes in the cells.

After total-body irradiation with threshold cataract-producing doses, the lens opacities may, after a certain time, be the only remaining 'clinical' and morphologic sign of the radiation injury. This is in conformity with SHIGETO and MASUDA's conclusions following their clinical examination

of victims of total-body irradiation after the atom bomb explosion at Hiroshima. Their clinical examinations were performed from June 1953 up to February 1955, that is, at least 8 years after the total-body irradiation. Among 246 subjects who had been exposed to total-body irradiation from the bomb, and who exhibited no other signs of irradiation injury, these workers found lens opacities with the morphologic picture of radiation cataract in 48 (19.5 %).

SUMMARY

The effect of total-body roentgen irradiation has been studied in 16 rabbits over periods of from $3^1/_2$ to 24 months following doses of from 200 to 800 r. The radiosensitivity of the epithelium of the crystalline lens is very marked. The lens opacities after the irradiation were identical with those previously observed after local irradiation of the eye. After small cataract-producing doses the lens opacities may be the only remaining sign of injury.

ZUSAMMENFASSUNG

Der Effekt der Röntgenganzkörperbestrahlung wurde an 16 Kaninchen über einen Zeitraum von $3^1/_2$ bis 24 Monaten bei Anwendung von 200 bis 800 r studiert. Die Röntgenempfindlichkeit des Epithels der Linse ist sehr ausgesprochen. Die Linsentrübung nach der Bestrahlung war gleich solchen die früher nach lokaler Bestrahlung des Auges beobachtet wurden. Nach kleinen Dosen, welche Katarakte verursachen, kann die Linsentrübung das einzig überbleibende Zeichen des Schadens sein.

RÉSUMÉ

L'effet de l'irradiation roentgen totale du corps a été étudiée sur 16 lapins, sur des périodes de $3^1/_2$ à 24 mois après des doses de 200 à 800 r. La radiosensibilité de l'épithélium de la lentille du cristallin est très marquée. Les opacités cristalliniennes après l'irradiation ont été identiques à celles observées auparavant après irradiation locale de l'œil. Après de petites doses produisant la cataracte, les opacités cristalliniennes peuvent être le seul signe persistant de l'irradiation.

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EXPERIMENTAL INVESTIGATIONS ON THE INFLUENCE OF ROENTGEN IRRADIATION ON THE GROWTH OF MULTIPLE TUMOURS

by

Antero Voutilainen

This work was carried out with the object of studying whether irradiation releases or activates any substance having an inhibitory effect on homologous, untreated tumour tissue. It has been demonstrated in previous studies that the tissues contain factors stimulating and inhibiting mitotic activity (6) and it was considered possible that active energy might influence these factors in some way. A transplantable experimental tumour was chosen as a suitable object of study and it was decided to transplant it into two sites in the experimental animal and irradiate one portion, growth phenomena being observed in the other, non-irradiated part.

Material and methods

Rat ITB tumour (8), which is easy to transplant (5), was available for the study. The experimental animals were 3 months old. Tumour tissue was transplanted subcutaneously into two sites in the back — the interscapular and the gluteal region. When the tumours had attained a size of about 3 cm diameter, the upper tumour was irradiated. The rats were anesthetized with ether and enclosed in a lead capsule, 2.0 mm in thickness, with an opening, the size of the tumour, for irradiation therapy. The Stabilivolt-Siemens apparatus of the Institute of Radiotherapy was used. The rats were irradiated at a 0.5 cm depth for 10 successive days, the dose being 500 r daily (140 kV, 10 mA, 5 mm Al filter, distance 30 cm, radiation field 3 × 6 cm). The superficial tumour dose was 135 r/min, the 0.5 cm depth dose 110 r/min, and the H. V. L. 0.28 mm^3. The 2 mm lead was entirely adequate for shielding the other

Supported by the Sigrid Jusélius Foundation and Damon Runyon Memorial Fund (DRG 291). Submitted for publication 27 June 1956.

tumour and the rest of the rat's body; measurements showed that less than 5 % of the roentgen rays penetrated a lead plate 1 mm thick.

After each treatment the volumes (length × breadth × height) of both tumours were always measured and the weight of the rats was recorded. In addition to the irradiated rats, the study included a control group, the multiple tumours in which were followed in the same way. Biopsy specimens were taken from all tumours at the commencement of treatment and after 5 and 10 days, at 6 p. m. The number of mitoses per 2,000 cells was determined from these specimens. The experiments were carried out in three series, the first comprising 3 irradiated rats and 3 non-irradiated controls; in the second and third series the figures were 5 and 5, and 8 and 7, respectively.

Experiments and Conclusions

Tumour volumes. For a graphic description of the changes occurring in the volumes of the tumours with the passage of time, the average volumes were first determined for the different groups, *viz.* the tumours of the irradiated rats, and those of the non-irradiated controls, a total of 4 groups. The above 3 experimental series were combined, and two average series of tumour volumes (A and B), expressed as the function of time, were thus obtained. Series A included all tumours, numbering 62 at the institution of treatment, and 40 on termination of treatment, the rest of the experimental animals having died in the interval. Series B included only the tumours of the surviving rats; as stated already their number was 40. The variations in the growth of tumours appear in Diagrams 1 and 2; the curves are similar in all groups except for a small depression in all curves of Diagram 1 at the 6th and 7th day, which is due to the fact that most of the deaths occurred at this time. For this reason Diagram 2 gives a clearer picture of the growth variations. It shows that the average volume of the non-irradiated tumours of the irradiated rats was 23.1 at the commencement of treatment and 30.4 at its termination. In the curve for the gluteal tumours of the controls the corresponding figures are 18.4 and 37.1. Both diagrams also show that growth was less in the gluteal tumours — a fact evidently due to greater tautness of the skin in the gluteal region.

A clearer picture was obtained of the variation in tumour growth by determining the growth function after the method of the least squares. For this purpose, a semilogarithmic system of coordinates was set up in which

$$\log \frac{\overline{V}}{10} \quad (\overline{V} = \text{average volume})$$

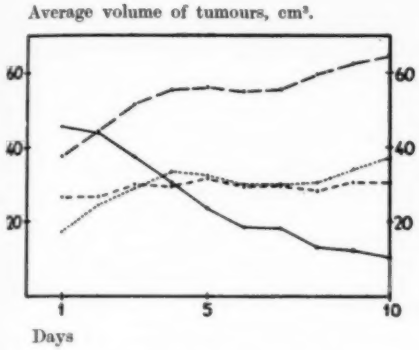

Diagram 1. Series A. Variations in tumour growth during irradiation treatment: all tumours.

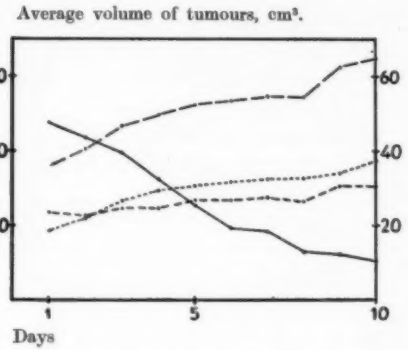

Diagram 2. Series B. Variations in tumour growth in the rats surviving treatment.

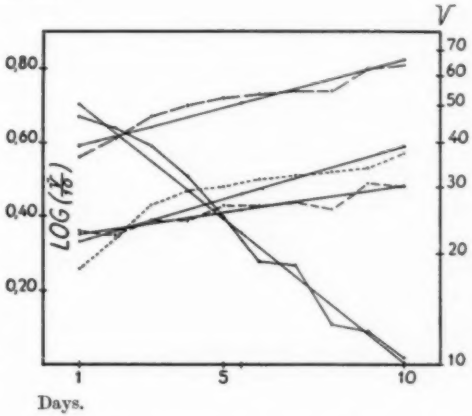

Diagram 3. Changes in average tumour volumes of surviving rats as expressed in a semilogarithmic system of coordinates. Linear trends were determined by the method of the least squares.

———— = irradiated tumour. - - - - - - - - = irradiated rats, non-irradiated tumour.
— — — — = interscapular tumour, non-irradiated rats. . . . . = gluteal tumour, non-irradiated rats.

was presented as the function of treatment days (Diagram 3). Its values were: for the non-irradiated tumours of the irradiated rats, 0.36 at the beginning of treatment, and 0.48 at the end of treatment; for the gluteal tumours of the non-irradiated rats, 0.26 and 0.57 respectively.

Calculated as above, the average growth percentage per treatment day was: — 8.6 in the group of irradiated tumours; + 3.0 for the non-

irradiated interscapular tumours; + 1.7 for the gluteal tumours of the irradiated rats; + 3.3 for the gluteal tumours of the non-irradiated rats.

The effect of irradiation during the 10-day period was also studied, using covariance analysis. Thus, the effect of the differences in initial volumes were eliminated from the 10-day variations in volume in the different groups. The following averages and standard errors were obtained (Table 1).

Table 1

Variations in adjusted average tumour volumes during 10 days of treatment. (The figures were adjusted to conform to the volume 30.75 on the first day)

	Irradiated rats				Non-irradiated rats			
	No	Interscap. irrad. tumour $cm^3 \pm SE$	No	Gluteal-non irrad. tumour $cm^3 \pm SE$	No	Interscap. tumour $cm^3 \pm SE$	No	Gluteal tumour $cm^3 \pm SE$
1st treatment day	9	47.14 ± 4.9	9	23.14 ± 4.9	11	35.92 ± 4.4	11	18.38 ± 4.4
10th » »	9	10.50 ± 4.5	9	30.44 ± 4.5	11	64.95 ± 4.1	11	39.81 ± 4.1
Adjusted vol. of 10th day.....	9	1.57 ± 3.7	9	34.59 ± 3.7	11	62.13 ± 3.3	11	46.55 ± 3.3

As would be expected, the average volumes of the irradiated tumours were significantly smaller ($P < 0.001$) than the average volumes of the non-irradiated tumours of the same rats, and of both tumours of the non-irradiated rats. It is interesting to note that the average volume of the non-irradiated gluteal tumours of the irradiated rats was significantly smaller than those of the gluteal tumours ($P < 0.02$) and interscapular tumours ($P < 0.001$) of the non-irradiated rats. A proportional comparison of the groups was also made by determining the average change, expressed as a percentage, during 10 days of treatment; the difference between the non-irradiated gluteal tumour of an irradiated rat and the gluteal tumour of a non-irradiated rat was highly significant ($P < 0.001$).

The study showed that, when one of two tumours transplanted into rats is irradiated, the growth of the non-irradiated tumour is also much slower compared with the same tumour in non-irradiated rats, the difference being significant. Irradiation has an inhibiting effect on its growth.

Mitoses. For comparing the variations in mitotic activity during irradiation, the series were combined as in the volume studies, and the average mitotic values were calculated for the different groups. At the beginning of treatment, the average mitotic value for the irradiated tumours was 85.9, and for the interscapular tumours of the non-irradiated rats 74.7; for the gluteal tumours the figures were 86.8 and 80.8 respectively. The mitotic values were computed from a total of 61 tumours. Table 2 shows the average mitotic values calculated 5 and 10 days after

Table 2

Adjusted average mitotic indices after 5 and 10 days of treatment. (The figures were adjusted to a level corresponding to the average mitotic value 85.9 for the irradiated tumours at start of treatment)

	Irradiated rats				Non-irradiated rats			
	Irradiated interscap. tumour		Non-irradiated Gluteal tumour		Interscap. tumour		Gluteal tumour	
	No	Mean of mitotic indices ± SE	No	Mean of mitotic indices ± SE	No	Mean of mitotic indices ± SE	No	Mean of mitotic indices ± SE
5 Days	15	16.2 ± 7.0	13	59.3 ± 7.6	14	91.8 ± 7.3	13	89.9 ± 7.6
10 »	9	0	9	70.0 ± 7.2	11	95.9 ± 6.6	11	89.0 ± 6.6

commencement of treatment; these values have been adjusted to conform to the initial value 85.9.

The differences in significance of the average mitotic values of the various tumours were studied by covariance analysis 5 and 10 days after the start of treatment. After 5 days already, the average mitotic value of the irradiated tumours was much smaller than the corresponding averages for the non-irradiated tumours of the same rats, and for both tumours of the non-irradiated rats, the difference being highly significant ($P < 0.001$). After 10 days, no mitotic values were noted in any of the irradiated tumours. Most important, however, was the finding that the average mitotic values for the non-irradiated gluteal tumours of the irradiated rats were significantly smaller than those for the gluteal tumours ($P < 0.002$ after 5 days and $P < 0.02$ after 10 days) and interscapular tumours of the non-irradiated controls ($P < 0.001$ after 5 days and $P < 0.005$ after 10 days). Thus the results were similar to those obtained in the volume measurements, *i. e.* the tumour inhibiting effect of irradiation was clearly apparent as a decrease in mitotic activity.

During treatment, none of the gluteal tumours of the irradiated rats healed. After the experiment, all the rats except for one irradiated animal and one non-irradiated control were decapitated. The volume of the gluteal tumour in the former was then 22 cm³, and after one week 41 cm³. The tumour then began to diminish, its volume being 32 cm³ after 2 weeks; 3½ weeks after the termination of treatment it had disappeared completely, leaving only a slight suppurating ulceration. Rapid epithelization of the ulcer followed and the rat recovered. Both tumours of the control rat continued to increase in size, the general condition of the animal rapidly declined, and it was therefore decapitated 9 days after the termination of treatment.

It is not easy to disclose the possible causes of this tumour inhibiting effect. However, the conception readily arises that irradiation liberates or activates some substance which has an inhibitory effect and which, evidently through the blood stream, can affect the other, non-irradiated

tumour. In favour of this last possibility are the results of studies in which tissue extracts were injected into tissues homologous with the source of the extract; the injection influenced mitotic activity (6.10). The effect exerted through the blood stream may be of a similar nature as that observed in parabiotic rats after performing a partial hepatectomy on one of the rats; this resulted in marked stimulation of mitotic activity in both the partially removed liver and in the non-operated liver of the other parabiotic rat (3).

FRIEDRICH-FREKSA and ZAKI (1954) injected serum from partially hepatectomized rats into normal rats and obtained a considerable increase in mitotic activity in the liver (4). Probably the question here is of regulation of growth by organ-specific substances. The blood was evidently the indirect causal factor in VAN DYKE's and HUFF's (9) experiment. For the purpose of producing epilation they irradiated the skin of one rat with 900 r, shielding the other rat with a lead plate. About 4 weeks after the irradiation, epilation was observed in both rats, and there was more hair growth in the non-irradiated one. Parabiotic rats have a joint blood circulation, and the active substance causing the epilation had evidently been transmitted from the irradiated to the non-irradiated rat.

The result of the investigation indicates a possible tissue specificity. This is also supported by an observation of TEIR and VOUTILAINEN (7); after the drying of irradiated tumour tissue, it was possible to prepare from it extracts having a cytolytic effect when injected into experimental animals following transplantation of homologous tumour tissue into these latter. In these experiments, a regression of the tumour was noted in 25 per cent.

In this connection it should be kept in mind that irradiation also has an indirect effect on tumour tissue; this is exerted through the surrounding healthy tissue and the entire organism. An important factor is certainly the skin; roentgen rays cause in it an inflammatory erythema and hyperthermia, which, on the basis of the experimental studies of BARTH, HUTH and WACHSMANN, retards the growth of tumour tissue (1). YAMAMOTO, as early as 1928, transplanted myxosarcoma subcutaneously into rats' thighs; one thigh was treated with a tumour dose of roentgen, the other being carefully shielded from irradiation. In 11 cases out of 20, the tumours decreased in size also on the non-irradiated side, in 3 cases there was complete regression (11).

The theory has been put forward that so-called necrohormones (2), stimulating cell division and multiplication may be produced in connection with tissue destruction. In high concentrations these necrohormones are specific cell toxins. It is possible that the above tissue-

specific stimulators of mitotic activity are substances similar to the necrohormones, and that they are activated by roentgen irradiation.

The possibility must also be taken into consideration that massive doses of roentgen impair the general condition so as to reduce the growth tendency of non-irradiated tumours. In the present study the decrease in average weight of the irradiated rats during treatment was — 29 g, the corresponding figure for the non-irradiated rats being — 6 g. The number of irradiated rats that died during this period was 7, as against 4 deaths in the control group. The smaller loss in weight in the controls is due to the continued growth of the tumours (Diagrams 1, 2, 3). It is possible, however, that some anti-growth factor is released as a result of irradiation. As early as 5 days after the institution of treatment, mitotic activity was significantly smaller also in the non-irradiated tumours of the irradiated rats. Another fact which abundantly supports the above possibility is the recovery of the one tumour rat, which took place $3^1/_2$ weeks after the end of treatment. The hair growth mentioned above appeared in the parabiotic rats after approximately the same period. These observations, again, favour the view that the majority of the highly complex radiobiologic chains of reaction do not terminate until a fairly long time has passed.

SUMMARY

The effect of roentgen irradiation on multiple ITB tumours transplanted subcutaneously into rats has been studied. A tumour in the interscapular region was irradiated with ten daily doses of 500 r, and growth phenomena were followed in a non-irradiated tumour in the gluteal region. The growth of this latter was inhibited, its size being significantly smaller after 10 days of treatment than that of a corresponding tumour in a non-irradiated control rat; in addition, mitotic activity was found to be significantly less both 5 and 10 days after the commencement of treatment. It may thus be assumed that some tumour inhibiting factor is released from or activated by the irradiated tumour.

ZUSAMMENFASSUNG

Die Wirkung der Röntgenstrahlen auf multiple ITB-Tumoren, welche bei Ratten subkutan transplantiert wurden, ist untersucht worden. Ein Tumor in der Regio interscapularis wurde mit 10 täglichen Dosen von 500 r bestrahlt und der Verlauf des Wachstums wurde an einem nicht bestrahlten Tumor in der Regio glutaealis beobachtet. Das Wachstum des zuletzt genannten Tumors wurde gehemmt, seine Grösse war nach 10-tägiger Behandlung signifikativ kleiner als die eines entsprechenden Tumors einer nicht bestrahlten Kontrollratte; ausserdem fand man, dass die Mitosenaktivität sowohl 5 als auch 10 Tage nach Beginn der Behandlung signifikativ geringer war. Es darf daher angenommen werden, dass ein das Tumorwachstum hemmender Faktor durch den bestrahlten Tumor freigemacht oder aktiviert wird.

RÉSUMÉ

L'auteur a étudié chez des rats l'effet de l'irradiation roentgen sur des tumeurs ITB multiples transplantées sous la peau. Une tumeur de la région interscapulaire a reçu dix doses quotidiennes de 500 r, et on a observé la croissance d'une tumeur non irradiée de la région fessière. Sa croissance a été inhibée, ses dimensions étant notablement inférieures, au bout de 10 jours de traitement, à celles d'une tumeur correspondante chez un rat témoin non irradié; en outre, l'activité mitotique a été trouvée notablement moindre 5 jours et 10 jours aprés le début du traitement. On peut donc supposer que la tumeur irradiée libère ou active un facteur inhibant les tumeurs.

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IN VIVO MEASUREMENT OF ORGAN SIZE USING A GAMMA RADIOACTIVE POINT SOURCE ('SCINTILLOMETRY') WITH SPECIAL REFERENCE TO APPLICATIONS IN GYNECOLOGY AND OBSTETRICS

by

Erik Odeblad, Sven Erik Englund,
and *Leo Meurman*

The measurement of certain linear distances in vivo is of considerable clinical interest and may often be performed by direct measurements or roentgen techniques. However, it may be of interest for the clinician to obtain rapid determinations of this kind in cases where these methods are usually not applicable, for example in the measurement of the size of the uterus or pelvic tumours. For such and similar cases we have developed a simple method based on the inverse square law and exponential transmission function for nuclear gamma rays. The principle used is shown schematically in Fig. 1.

Theoretical aspects. Consider a point source of gamma radiation at a distance D from a radiation detector (most conveniently a scintillation detector). The impulse rate in the detector, i, is then

$$i = I \cdot T(D)/D^2 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

$T(D)$, being the transmission function. For a considerable part of a single gamma ray transmission function it is exponential, so that we may write

$$i = I \cdot \exp\ (-\mu D)/D^2 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

This expression is equivalent to the point source matrix element in the matrix theory of in vivo measurements (ODEBLAD 1956). In these equations, I is the impulse rate at unit distance without absorption and μ the total gamma ray (photoelectric, Compton and pair creation) absorption coefficient. If equation (2) is written in a logarithmic form we obtain

$$\log i = \log I - \mu D \log e - 2 \log D \quad \ldots\ldots\ldots\ldots\ldots \quad (3)$$

Submitted for publication 27 July 1956.

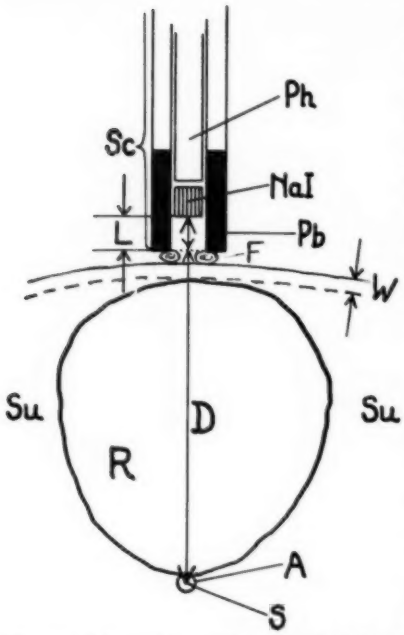

Fig. 1. Schematic outline of principle of measurement. *S* = source of gamma radiation with absorber (*A*) for beta rays. *R* = resistance to be measured. *D* = distance primarily obtained, including size of resistance, abdominal wall (*W*), palpating fingers (*F*) and beta absorber (*A*). *L* = collimator length. *Su* = surroundings. *NaI* = sodium iodide crystal. *Ph* = photomultiplier tube, *Sc* = scintillation detector.

Eq. (3) implies that if the data are plotted in a double logarithmic coordinate system (of log i against log D) a straight line would result, presuming no absorption of gamma rays. In general, it is desirable to employ gamma radiation with as small absorption coefficient as possible. Deviation from eq. (3) is to be expected due to edge-effects in the scintillating crystal, contribution from scattered gamma radiation, etc. The use of appropriate calibration curves and model experiments are therefore always necessary so that the method will be founded on sufficient empirical data.

Choice of radioactive source. Several factors govern the choice of the most suitable source of radiation. The most important are the following.

1. Energy. As just mentioned, the total absorption coefficient, μ, should be as small as possible. In diagram 1, μ is plotted against quantum energy of gamma rays. The energy range between 1 and 10 MeV implies minimum values in tissues of total absorption coefficient. This suitable energy range implies, however, a low efficiency, p, in scintillation counting, as is also indicated in the diagram.

2. Half-life. It is desirable to use an isotope with a half-life sufficiently long so that the activity does not appreciably fall off within months or years. A very long half-life, on the other hand, requires a very long activation time in the pile to induce enough radioactivity; the most suitable half-life therefore seems to be in the range roughly between $^1/_{10}$ and 100 years.

3. Neutron activation cross-section. The radioactive source must be formed with a cross-section high enough (over about 1 barn) on a conveniently available element in order to obtain sufficient specific activity.

4. Beta radiation. The presence of beta radiation may cause a very high local roentgen dose around the source. It is therefore important that the beta decay of the radio-isotope proceeds with low energy electron or positron decay or with electron capture. This last type of decay may

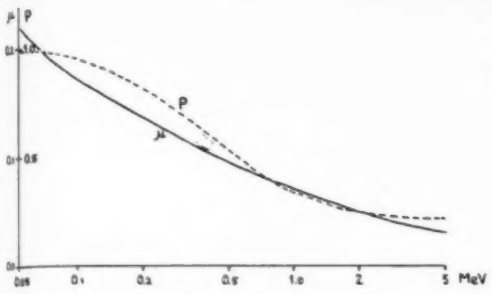

Diagram 1. Relation between gamma ray energy, total absorption coefficient, μ, and efficiency, p, of scintillating crystal (2.5 × 2.5 × 2.5 cm, cylindrical). Mainly from DAVISSON (1955) and BELL (1955) with minor modifications.

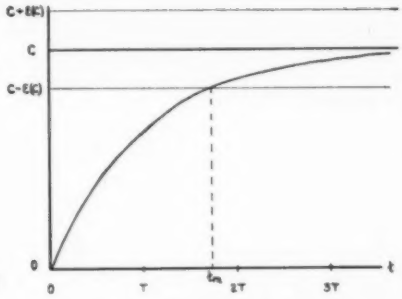

Diagram 2. Ratemeter deflection plotted against time, t, c = equilibrium deflection. T = time constant. Ordinate = counts per min; abscissa: time in min. The lines $c \pm \varepsilon(c)$ give statistical error in c. t_m denotes the point of time when the exponential ratem deflection curve intersects line $c - \varepsilon(c)$.

be associated with a low energy roentgen radiation giving a fairly high local tissue dose around the source.

5. Complexity of decay scheme. It is theoretically and practically advisable that the gamma ray branches in the decay scheme are not too many and do not contain very low energy components.

Some radio-isotopes having suitable properties in these respects are given in Table 1. We have elected to use Co^{60} as the most convenient gamma ray source in our studies.

Sources of error. Several sources of error have to be taken into consideration. The most important are the following.

1. Statistical error in ratemeter impulse counting. The error $\varepsilon(n)$ in n counts is obtained from Poisson statistics and is $\sqrt{n}$. If c is the counting rate (min^{-1}) and T is the average time (min) of the impulse memory, which is equal to the time constant of the ratemeter, we have (for infinite time)

$$n = c \cdot \int_0^\infty e^{-t/T} dt = c \cdot T \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (4)$$

and

$$\varepsilon(n) = \sqrt{n} = \sqrt{c \cdot T} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (5)$$

Taking the derivate of equation (3) and replacing the differentials with the errors, we obtain

$$\frac{\varepsilon(D)}{D} = \frac{1}{(\mu D + 2)\sqrt{cT}} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (6)$$

If the average counting rate is equal to 10^4 min^{-1} and $T = 1/6$ min, $D = 10$ cm, and $\mu = 0.063$ (for Co^{60} radiation in tissues), we obtain for $\varepsilon(D)$ the value of 0.1 cm

Table 1

Radio-isotope	Half-life	Percentage and energy of beta rays MeV	Percentage and energy of gamma rays MeV	p (Approxi-mate)	μ for H_2O (average) cm^2/g or cm^{-1} approxi-mate	Suitable amount in source (maximum)
Na^{22}	2.6 years	0.54 (89 %) EC (11 %) 1.8 (0.01 %)	0.51 (178 %) annihilation 1.28 (~ 100 %)	2.8 × 0.50	0.08	15 μC
Co^{60}	5.3 years	0.31 (100 %) 1.5 (0.1 %)	1.33 (~ 100 %) 1.17 (~ 100 %)	2 × 0.30	0.063	25 μC
Zn^{65}	245 days	0.32 (~ 2 %) EC 98 %, two branches	1.12 (~ 55 %) 0.50 (~ 4 %) annihilation	0.6 × 0.35	0.070	80 μC
Cs^{137}	37 years	0.51 (92 %) 1.17 (8 %)	0.66 (~ 92 %)	0.9 × 0.45	0.87	40 μC
Tm^{170}	129 days	0.97 (~ 97 %) 0.88 (~ 3 %)	0.085 (~ 3 %) conversion	0.03 × 0.95	0.18	200 μC
Hg^{203}	45 days	0.21 (100 %)	0.28 (85 %) (conversion 15 %)	0.85 × 0.90	0.12	100 μC

Data mainly from HOLLANDER, PERLMAN and SEABORG (1953).

or 1 per cent. The errors of random impulse distribution is therefore of the order of millimetres.

2. Ratemeter equilibration. Under otherwise constant conditions, the ratemeter deflection approaches an equilibrium value c exponentially as indicated in Diagram 2.

$$c_t = c\,(1 - e^{-(t/T)}) \quad \ldots\ldots (7)$$

Here c_t is the ratemeter deflection at time t (expressed in min), c the equilibrium deflection in min^{-1}, and T the time constant in min. The point of time, t_m, when

$$e^{-(t/T)} < \varepsilon(n)/n \quad \ldots\ldots (8)$$

gives the practical equilibration time of the ratemeter before the reading. Introducing eq. (5) we obtain

$$e^{(t_m/T)} > \sqrt{cT} \quad \ldots\ldots (9)$$

or

$$t_m > (T/0.87)\ \log\ (cT) \quad \ldots\ldots (10)$$

Introducing the average values used earlier ($c = 10^4$ min^{-1} and $T = 1/6$ min) we obtain $t_m > 0.6$ min. It is of little use to extend the time of equilibration much further because the statistical error and other errors then completely dominate. Minor ratemeter deflection unstabilities should be disregarded.

3. Compton scattering. One important factor influencing the measurements is the scattering of gamma rays due to the Compton effect. Consider a small volume element $dR \cdot dY$ (Fig. 2) seen under the solid angle $\frac{dY}{4\,\pi R^2}$ from the source, and let $\sigma\,(E, w)$ denote the energy dependent differential cross-section. We obtain for the counting rate $c\,(c = p \cdot i)$

$$d^2c = p \cdot S \cdot 1.85 \cdot 10^4 \cdot (\Sigma NZ) \cdot (e^{-\mu R} dR/R) \cdot \sigma(E,w)\ \sin\ w dw \cdot e^{-\mu R} \ldots\ldots (11)$$

Here S is the strength of source in μC and (ΣNZ) the electrons/cm³ of scattering tissue element. Representative relative values of (ΣNZ) are given in Table 2; (ΣNZ) for water is $3.4 \cdot 10^{23}$ electrons/cm³ $\cdot \mu$ and μ' are obtained from Diagram 1. B is given by the cosine theorem

$$B^2 = D^2 + R^2 - 2\,DR\cos\beta, \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (12)$$

and β by the sine theorem

$$\frac{\sin\beta}{B} = \frac{\sin w}{D} = \frac{\sin(\beta + w)}{R}; \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (13)$$

$\sigma(E, w)$ is obtained from the KLEIN and NISHINA (1929) equation in cm²/(electron · ·steradian):

$$\sigma(E, w) = \sigma_1 \frac{1 + b^2}{[1 + q(1 - b)]^2}\left[1 + \frac{q^2(1 - b)^2}{(1 + b^2)(1 + q - qb)}\right]. \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (14)$$

$q = E/mc^2$ and $b = \cos w$. $\sigma_1 = e^4/2(mc^2)^2$; e being the electronic charge and mc^2 the electronic rest mass. Summation is carried out for all fractions of gamma decay in the decay scheme. Energy E' of secondary gamma ray is given by

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Eqs. (11) to (15) clearly show that the tissues between the source and detector are most important in producing Compton effects which add to the measured radiation flux.

Eq. (11) may be integrated explicitly for various geometrical situations but this is usually difficult both theoretically and numerically. Actual measurements on phantoms in model experiments will therefore be the most practical method.

In the measurement of pelvic distances with the present method, as compared with phantom measurements, there are two main factors that influence the results, the Compton effect on intestinal gas and on pelvic bone. Of these two factors the gas in the intestines is the most varying one. Good collimation of the beam reduces the influence of varying contributions from scattering.

With the schematic outline of pelvic geometry in view, as given in Fig. 4, measurements were undertaken on a water phantom, introducing gas-filled vessels of simulated appropriate size and shape. Some results are shown in Table 3.

The phantom experiments indicate that the errors due to uncorrected Compton scattering effect may contribute up to about 5 per cent to the distance measured.

4. Influence of the abdominal wall. The abdominal wall varies in thickness in different cases and implies therefore a source of error. In addition, the fingers palpating the fundus and the scintillation detector may compress the wall.

In suitable cases it is possible to measure the thickness of the abdominal wall, as is shown in Fig. 4, using a weak source. In other cases the thickness of the abdominal wall can only be estimated. When repeated measurements are undertaken in a single case to determine *e. g.* changes in uterine size in the puerperium, or in different ages, the influence of the abdominal wall is of small importance.

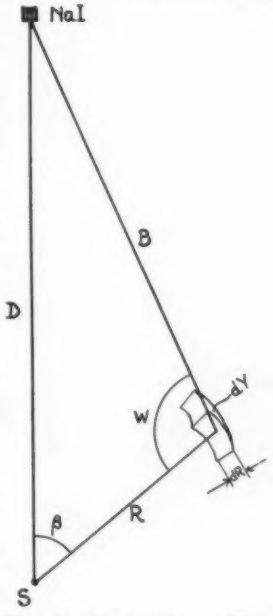

Fig. 2. Schematic outline of the origin of disturbing Compton scattered radiation from a scattering element $dR \cdot dY$. S = source of gamma radiation. NaI = detecting crystal. This figure also defines lines D, B and R, the angle β and scattering angle, w.

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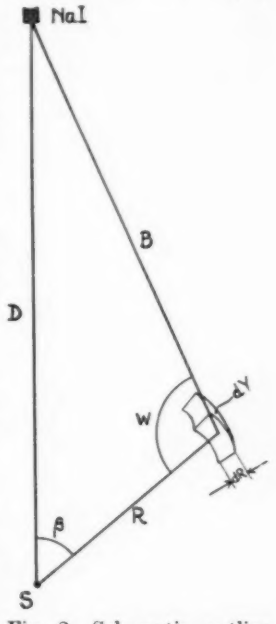

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Table 2

Electron densities (water 1.00) for some important substances

Substance	Relative electron density
Water	1.00
Myometrium	1.02
Contents of ovarian cyst	1.02
Air	0.001
Bone (average)	1.70
Ascitic fluid	1.01

The error contributed by the abdominal wall may vary from case to case, from about 0.5 to several centimetres when the abdominal wall is very thick or soft.

5. Deformation of the organ subjected to measurement. Too great a pressure may cause deformation of the uterus, or a pelvic tumour, so that the value measured is not representative for the intact organ *in vivo*. An error amounting to 0.5 to 1 cm may result in solid, and several centimetres in soft or cystic tumours, or organs. (Regarding the influence of uterine flexion, see discussion.)

The combined action of these errors is difficult to estimate. A minimum error of 0.5 cm may be regarded as probable for uteri or solid tumours of 10 cm linear dimension in very favourable cases. In large soft resistances, or in unfavourable conditions due to the abdominal wall, errors up to 2 cm or more may result from the contributions of all errors.

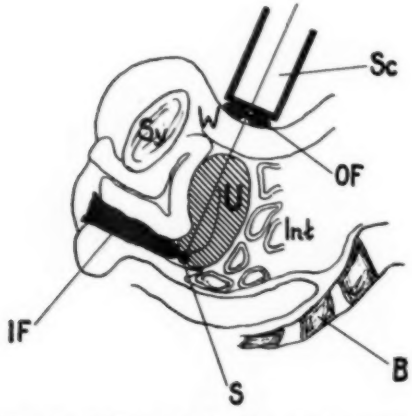

Fig. 3. Outline of situation during measurement. *U* = uterus, *W* = abdominal wall, *Int* = intestine, *Sy* = symphysis, *B* = bony pelvis, *S* = source of radiation, *IF* = inner finger, *Sc* = Scintillation detector, *OF* = outer fingers. Other position of source is indicated in Fig. 5.

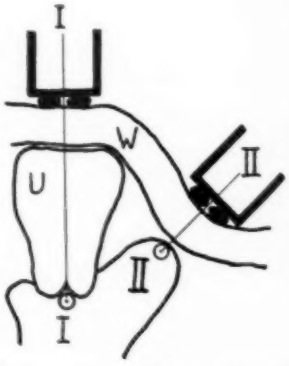

Fig. 4. Approximate measurement of thickness of abdominal wall (*W*) including vaginal wall and parametrium (Position II) for correction of measurement of uterus (*U*) in Position I.

Table 3

Simulated intestinal gas filling on phantom	Relative counting rate
No gas	1.00
Moderate gas filling	0.96
Extensive gas filling	0.89

Radiation dose

For Co^{60} the dose rate of about 1.35 mr/hr at 1 m distance, per mC, is established theoretically from γ ray absorption coefficients in water (DAVISSON 1955) and supported by experimental measurements (see *e. g.* MAYNEORD 1950). This corresponds to 0.24 mr/min 1 cm from a 1 μC Co^{60} source. Since the radius of shielding around the point source was 0.4 cm, and the common source strength 5 μC, the dose rate at the closest part of cervical and vaginal tissues was about 10 mr/min. This is also the highest dose rate at the finger of the investigator. Since the examination usually takes no longer than about 1 to 2 minutes (minimum time = 0.6 min as discussed above), the dose to the patient is negligible. If the patient should be pregnant, the average dose rate to the fetus is 1 to 2 mr/min, also a negligible dose rate (see *e. g.* the review by RUGH 1953, and references therein). The dose rate on the ovaries may vary between 0.3 and 5 mr/min. Except for cases of legal abortion we have not performed measurements in pregnancy, or when pregnancy could not be excluded.

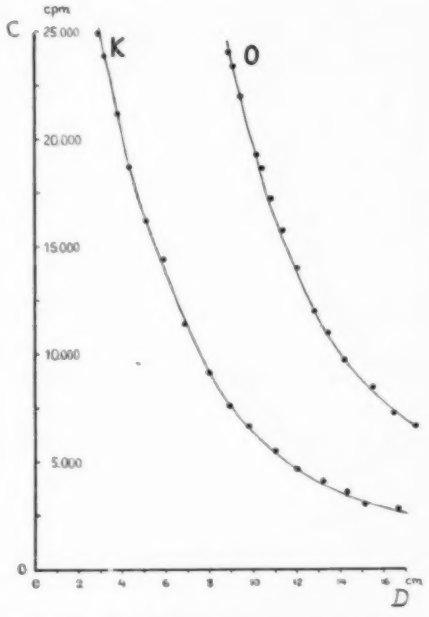

Diagram 3. Relation between counting rate (*C*) and distance (*D*) in water phantom with (*K*) and without (*O*) collimator for one of the sources used.

Arrangement for measurements. Sources of radiation between 2 and 10 μC of Co^{60} in liquid form were kept in thick-wall glass tubes. They were introduced inside the rubber glove at the side or at the top of the palpating vaginal finger.

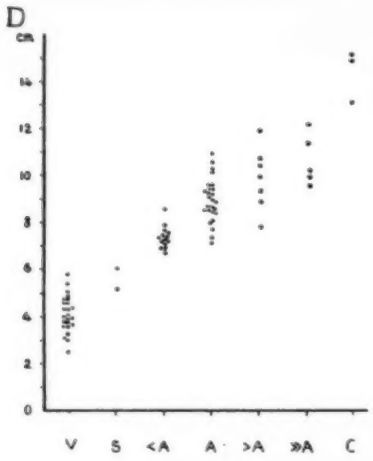

Diagram 4. Relation between bimanually estimated and scintillometrically measured uterine size in cm. A = size of adult uterus, $< A$ = slightly less than A, $> A$ = slightly larger than A, $\gg A$ considerably enlarged uterus, C = uterus enlarged to about the size of an infant's head, S = uterine stump after hysterectomy or comparable size, V=vaginal wall and parametrium (= Position II in Fig. 4). Ordinates also include abdominal wall and palpating fingers. Mean values and standard deviations are presented in Table 4.

The equipment for the detection of gamma rays consisted of a shielded directional scintillation counter (see Fig. 1). The impulse rate was read directly on a ratemeter or counted on a scaler. The use of a ratemeter was usually preferred since it allowed an easy adjustment of an optimum direction of the collimator.

Results of model experiments (calibration curves). Measurements were undertaken on water phantoms. Some results are shown in Diagram 3. As mentioned above, other experiments were designed to measure the influence of gas filling of the intestinal canal and bony pelvis. Some of these experiments are given in Table 3.

Results of some clinical applications. In Diagram 4 and Table 4, results are collected showing relations between bimanually estimated and measured sizes of the uterus. In Diagram 5, results are presented of relations between operatively controlled and measured size of uterus.

Discussion.

The theoretical interpretation as well as the practical results in model experiments and clinical practice indicate that the non-destructive method proposed here may be of value in obtaining an objective measure of the size of the uterus or other pelvic resistance. There has been a widespread practice in gynecology to describe the size of the uterus and other pelvic resistances by comparison with well-known objects of appropriate size and shape, for example a hen's egg.

In order to realize a more reproducible determination of the size of normal and pathologic pelvic resistances, more exact methods have to be introduced. The method proposed here may be regarded as one among other such methods, and we hope it may be of some value in certain cases, *e. g.* in the control of the growth of pelvic resistances, in repeated examinations, in the diagnosis of uterine hypoplasia, studies on the involution of the uterus, and especially for affording an objective and reproducible assessment of uterine size from different observers.

Table 4

Statistics of values of D, presented in Diagram 4

Group	D_{mean} and variation	Number of observations	Individual diff-erences ($D - D_V$) mean and variation	Number of observations
V	4.8 ± 0.8 (σ)	24	—	—
S	5.4 ± 0.4 (m)	2	—	—
< A	7.3 ± 0.6 (σ)	14	3.4 ± 0.4 (σ)	9
A	8.9 ± 0.9 (σ)	26	4.8 ± 0.5 (σ)	17
> A	9.8 ± 1.2 (σ)	7	5.7 ± 0.7 (σ)	6
> A	10.6 ± 1.5 (m)	5	—	—
C	14.6 ± 1.6 (m)	3	—	—

σ = dispersion (standard deviation), m = maximum error.

It should be pointed out that the method proposed may in principle also be used in regions outside the pelvis.

In the special application on the size of uterus dealt with in the present paper one complication arises from the flexion of the uterus.

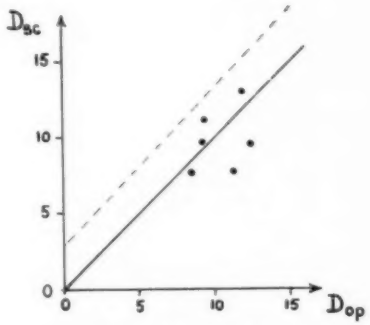

Diagram 5. Relation between operatively controlled uterine size and preoperatively measured uterine size. D_{sc} = scintillometrically measured uterine size (including vaginal wall and fingers), D_{op} = largest distance of stretched extirpated uterus. Dotted line gives the relation with correction for abdominal wall and palpating fingers.

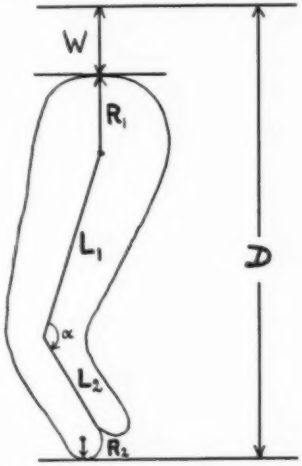

Fig. 5. Illustrating influence of uterine flexion. Distances L_1 and L_2 refer to corporal and cervical lengths, and R_1 and R_2 to the corresponding radii given in the figure. W is thickness of abdominal wall and α angle of flexion between corpus and cervix.

Consider Fig. 5 and the notations of distances given therein. The length we measure is D which is given approximately by the eq.

$$D = R_1 + R_2 + \sqrt{L_1^2 + L_2^2 - 2\ L_1\ L_2 \cdot \cos a} + W \quad \ldots\ldots\ldots\ (16)$$

where a is the angle of flexion of the uterus. The quantity $(L_1 + R_1)/(L_1 + R_1 + L_2 + R_2)$ is what is usually denoted the uterine index. Eq. (16) shows that when the flexion angle a is large, or between 135° and 180°, the error introduced by neglecting it may be small but may amount to — 0.9 cm in typical values for adult women. It is therefore necessary to try to obtain some information about the flexion angle of the uterus and to note if this angle is negligible or not. In case of retroflexion our method is usually not practicable.

The data collected in Diagram 4 indicate in effect that flexion of the uterus plays an important role in the measurements. Subtracting a contribution of about 1 cm for the vaginal wall and parametria from the values in Group V in Diagram 4, we obtain for the linear distance portiofundus 5.8 ± 0.5 cm (standard error), which is shorter than the length usually assigned to the normal uterus (7 cm). Assuming a uterine index of $^2/_3$ we obtain an average flexion angle, a, of about 100° in the normal cases investigated (Group A).

The data given in Diagram 5, where the measured uterine length is considerably shorter than the length of the stretched uterus, also indicate the importance of flexion. Here the pressure on the uterus during the scintillometric measurement may also contribute to make the values measured shorter than those obtained at direct measurement on the uterus after it was removed at operation.

We have found that different observers sometimes arrive at different values for D, these lying more apart than might be expected from the uncertainty inherent in the radio-isotope measuring technique. Such differences have been discussed between the various observers and have often been explained satisfactorily by inadvertencies in the technique of the bimanual examination, or more systematic differences in the technique. In that way scintillometry may aid in the assessment of the size of pelvic resistances, more than by the mere recording of conventional findings in gynecologic examinations.

SUMMARY

A method is described for the measurement *in vivo* of linear distances of organs, based mainly on the inverse square law and including perturbations due to absorption and scattering of gamma radiation. The organ is interposed between a point source of gamma radiation and a scintillation detector; the distances are read from calibration curves obtained by phantom experiments. The method is regarded as a step towards a more objective assessment of organ size than obtained in the gynecologic examination.

ZUSAMMENFASSUNG

Eine Methode zur Messung linearer Distanzen *in vivo* wird beschrieben. Die Methode benutzt das Gesetz der invertierten quadratischen Abnahme der Strahlung, die durch Absorption und Streuung modifiziert wird. Das Organ wird zwischen einer punktförmigen Gammastrahlenquelle und einen Scintillationsdetektor gebracht. Der Abstand wird mit Hilfe der Kalibrierungskurve am Phantom erhalten. Die Methode wird als Fortschritt zu einer exakteren und reproduzierbaren gynäkologischen Untersuchung betrachtet.

RÉSUMÉ

Les auteurs décrivent une méthode de mesure in vivo des dimensions linéaires des organes, basée principalement sur la loi de l'inverse du carré de la distance, et tenant compte des perturbations dues à l'absorption et à la diffusion des radiations gamma. L'organe est placé entre une source ponctuelle de radiations gamma et un compteur à scintillation, et on lit les distances sur des courbes d'étalonnage établies par des mesures sur fantôme. Cette méthode est considérée comme une étape vers une détermination des dimensions des organes plus objective que celle que fournit l'examen gynécologique.

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BOOK REVIEW

OBSERVATIONS ON THE MIGRATION OF CERTAIN LABELLED SUBSTANCES BETWEEN THE URINARY BLADDER AND THE BLOOD IN THE RABBIT. By Sven Erik Englund. 80 pp., 50 figs. and 2 tables. Acta radiol. Suppl. 135 (1956). Sw. Kr. 25: —.

An experimental work on problems dealing with migration of certain ions across the bladder mucosa in the rabbit is presented. The radioisotopes Na^{24}, P^{32}, K^{42}, Br^{82} were employed.

In a review of earlier literature special reference is given to investigations using radioisotopic tracer technics.

The radioisotopes and detection technics are described and special attention is paid throughout the work to the identification and standardization of the radioisotopes as well as to the errors which may occur.

The experimental investigations were undertaken with different technics. In one series of experiments the migration of radioisotopes from the bladder to the blood was studied by analyzing blood samples taken directly from an incised bladder vein. The rate of migration described a curve with a typical shape; the curve showing a rapid rise for about 1 to 12 minutes to a maximum and a slower decrease tending to a more or less constant level about 20 to 40 minutes after the start of the experiment. The peak value was about 2 to 8 times higher than that of the final level.

Several factors were investigated as to their possible effect on the characteristic appearance of the curve. The effects of anaesthesia, operative technic, and blood pressure were studied; none of these factors were apparently capable of altering the general type of the curve. In other experiments the effects of temperature, pH, radioisotope contents, and strength and type of solution in the bladder, were studied. None of these factors seemed to be of any great importance in governing the general shape of the curve. Nor did experiments on volume and pressure conditions in the urinary bladder afford any explanation for its general appearance.

In a second series of experiments the migration of radioisotopes from the blood to the bladder was determined. A continuously increasing activity in the bladder contents occurred.

A quantitative determination of the migration over the bladder mucosa was undertaken in spite of several difficulties. The penetration of Br^{82} from the bladder content to the blood was in order of ~ 0.01 % per minute in one vesical vein. Double tracer experiments using two different radioisotopes simultaneously, indicated the same order for Na^{24} and K^{42}, perhaps slightly less for P^{32} phosphate ions.

The migration of the different ions was small and it did not appear unreasonable to assume the existence of a barrier somewhere in the bladder mucosa. Further information was furnished by *in vivo* clearance experiments. These experiments showed the clearance of intramural deposits of Br^{82} to be considerably more rapid than that of intravesical deposits. Consequently it seemed probable that this barrier lies in the vicinity of or in the bladder epithelium. To confirm this assumption, the bladder mucosa was damaged by the intravesical introduction of turpentine. In these experiments the migration of radioactivity was greatly increased over that in undamaged bladders. This corroborates the view that a barrier to the penetration of certain substances exists, located close to or in the vesical epithelium.

In order to gain some insight into the phenomena described in the present work certain theoretic considerations are included.

Autoreview.